Chapter 80

# Near and Middle East

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The current chapter is a discussion of the epidemiology, causes, predisposing factors, management, and prevention of kidney diseases, and future strategies for dealing with kidney diseases in the Near and Middle East are proposed. The term *Near and Middle East* is a historical, Eurocentric, and Western term that was used to describe a geographic region whose boundary is imprecise and whose internal borders are constantly changing because of political and historical evolution.[1] Therefore, the Near and Middle East, hereafter called the *Middle East,* is defined for the purpose of this chapter as the region that encompasses the following 20 countries (in alphabetical order): Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestinian Authority, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, the United Arab Emirates (UAE), and Yemen (Figure 80-1).

The Middle East (ME) has always been important for (1) its strategic location as a tricontinental hub that links Asia, Africa, and Europe; (2) its economic resources; and (3) its spiritual significance as the birthplace of the world's three major monotheistic religions: Judaism, Christianity, and Islam. Of the adherents to the three religions, Muslims constitute the largest religious population in the ME; the sizes of the Christian and Jewish populations are smaller and vary from country to country in the ME.[1] Although the ME has several cultural, linguistic, and geographic associations, considerable disparity exists between the different countries in terms of economy, resources, political systems, health care systems and expenditure, and disease incidence and prevalence.

According to data from the World Health Organization (WHO),[1a] the estimated population in the 20 ME countries in 2009 was 451,084,000, and the median ages ranged between 18 and 31 years (Table 80-1). The gross national income (GNI) per capita varies for each ME country. According to the classification system of the World Bank,[1b,1c] most ME countries are considered "developing countries." Egypt, Iran, Iraq, Morocco, Syria, the Palestinian Authority, Tunisia, and Yemen are considered lower-middle-income countries because the GNI per capita of each is between $996 and $3945 (USD) per annum, whereas Algeria, Jordan, Lebanon, Libya, and Turkey are considered upper-middle-income countries because the GNI per capita of each is between $3946 and $12,195 per annum.[2] The following countries are considered high-income industrialized countries because the GNI per capita of each is more than $12,196 per annum: Bahrain, Israel, Kuwait, Oman, Qatar, Saudi Arabia, and UAE (Figure 80-2). Inevitably, disease incidence, prevalence, course, and outcomes are affected by the different socioeconomic factors and health policies in each country[2,3,4] (see Figure 80-2). For example, the life expectancy and infant mortality rate in each ME country are concordant with the socioeconomic, political, and health status of that country. The median life expectancy in the 20 ME countries ranges from 62 to 82 years for men and from 67 to 83 years for women; the life expectancy for men and women is lowest in the low-income ME countries and highest in the high-income, industrialized ME countries (see Table 80-1).

The mortality rate before the age of 5 years in Yemen, the poorest country in the ME, is at least 5 times higher (66 per 1000 live births) than that in industrialized ME countries (5 to 12 per 1000 live births; see Table 80-1). Also, a health disparity exists among minority populations who live in industrialized ME countries and individuals of ME origin who live in countries that are not in the ME.[4-8] Many developing ME countries have been affected by various types of natural disasters (such as earthquakes, floods, and droughts) and other disasters (such as military conflicts). Casualties, displacement, and migration are significant consequences of such disasters and adversely affect the socioeconomic stratum and health status of a country. Therefore, many ME countries

**FIGURE 80-1** Map of Middle Eastern countries. Countries illustrated in *light green* also known as "El Maghreb"; those in *dark green,* as "El Mashreq."[1] (Adapted and modified from a public domain image available at http://wikipedia.org.)

and their communities need help in upgrading their existing health structures in order to improve their ability to cope with any future disasters. Consequently, the WHO, together with national and international nephrology societies, such as International Society of Nephrology (ISN), have pooled their resources to enhance the resilience of nations to the effects and consequences of disasters.[9-12]

## Acute Kidney Injury

As in many countries worldwide, data on the incidence and prevalence of acute kidney injury (AKI) in many ME countries are scarce and imprecise because of an inconsistent definition of AKI in medical reports, underreporting, seasonal dependency on the occurrence of AKI, and the frequency and location of natural and human-engendered disasters.[9,13,14] There are large knowledge gaps about the age, number, natural history, and outcome of patients with AKI in either the community or hospitals and about the use of preventive measures in each ME country. Most published reports on AKI in ME countries have concerned a short-term study in a tertiary-level hospital or a single-center study, and of these studies, only a few were of the prospective type. Moreover, the definition of AKI is not consistent in these reports.[15-18] Al-Homrany[17] reported that the incidence of AKI among hospitalized patients was 0.6% in a 2-year prospective study in one hospital in southern Saudi Arabia. Of these cases of AKI, 62% were hospital acquired and 38% were community acquired. In a 1-year retrospective cohort study from a single center in northern Israel, Shema and associates[18] reported that the annual incidence rate of AKI among hospitalized adult patients was 1% to 5.1%, depending on the AKI definition that was used.

The causes of AKI have changed over time in ME countries. Obstructive uropathy, unspecified postsurgical complications, and crush injury were the most prevalent causes of AKI in Syria during the 1980s, according to Hadidy and colleagues.[15] Said[19] studied the causes of AKI in 215 patients with AKI, whose ages ranged between 12 and 90 years, in three Jordanian hospitals over an 18-month study period. The findings of this study were similar to those that have been published from industrialized countries, which are discussed in detail in Chapter 30. Said reported that renal parenchymal disease was the most common cause of AKI (58%), and acute tubular necrosis (ATN) and contrast-induced nephropathy were the two most prevalent causes of renal parenchymal disease. Prerenal causes (28%) and postrenal causes (14%) accounted for the remaining causes of AKI.[19] Of note, Said reported that obstructive uropathy was a common cause of

**TABLE 80-1 Demographic and Health Indicators in Middle Eastern Countries and Western Industrialized Countries**

| COUNTRY | TOTAL POPULATION | MEDIAN AGE (YEARS) | LIFE EXPECTANCY AT BIRTH (YEARS) | | RATE OF MORTALITY BEFORE AGE 5 YEARS (PER 1000 LIVE BIRTHS) |
|---|---|---|---|---|---|
| | | | MALE | FEMALE | |
| **Middle Eastern Countries** | | | | | |
| Algeria | 34,895,000 | 26 | 71 | 74 | 32 |
| Bahrain | 791,000 | 28 | 73 | 76 | 12 |
| Egypt | 82,999,000 | 24 | 69 | 73 | 21 |
| Iran | 74,196,000 | 26 | 70 | 75 | 31 |
| Iraq | 30,747,000 | 19 | 62 | 70 | 44 |
| Israel | 7,170,000 | 30 | 80 | 83 | 5 |
| Jordan | 6,316,000 | 22 | 69 | 74 | 25 |
| Kuwait | 2,985,000 | 30 | 78 | 79 | 13 |
| Lebanon | 4,224,000 | 29 | 71 | 77 | 12 |
| Libya | 6,420,000 | 26 | 70 | 75 | 19 |
| Morocco | 31,993,000 | 26 | 71 | 75 | 38 |
| Oman | 2,845,000 | 24 | 72 | 77 | 12 |
| Palestinian Authority | 3,200,000 | NA | NA | NA | NA |
| Qatar | 1,409,000 | 30 | 78 | 79 | 9 |
| Saudi Arabia | 25,721,000 | 24 | 69 | 75 | 21 |
| Syria | 21,906,000 | 22 | 71 | 76 | 16 |
| Tunisia | 10,272,000 | 29 | 73 | 77 | 21 |
| Turkey | 74,816,000 | 28 | 72 | 77 | 20 |
| United Arab Emirates | 4,599,000 | 31 | 77 | 79 | 7 |
| Yemen | 23,580,000 | 18 | 63 | 67 | 66 |
| **Western Countries** | | | | | |
| Australia | 21,293,000 | 38 | 80 | 84 | 5 |
| Canada | 33,573,000 | 40 | 79 | 83 | 6 |
| France | 62,343,000 | 40 | 78 | 85 | 4 |
| Germany | 82,167,000 | 44 | 78 | 83 | 4 |
| Italy | 59,870,000 | 43 | 79 | 84 | 4 |
| Japan | 127,156,000 | 44 | 80 | 86 | 3 |
| United Kingdom | 61,565,000 | 40 | 78 | 82 | 5 |
| United States | 314,659,000 | 36 | 76 | 81 | 8 |

*NA,* Not available.

Source data for country profiles from the World Health Organization: *Countries,* Available at: http://www.who.int/countries/en/. Accessed May 2011.

AKI as a result of the high prevalence of nephrolithiasis in the study patients who originally came from Yemen and Sudan. In another study from one center in Qatar, ATN was reported in 83% of all patients with AKI, who were referred mainly from intensive care units.[20] Al-Homrany[17] reported that ATN resulting from sepsis, ischemia, and rhabdomyolysis, as well as distinctive causes, such as malaria and snakebites (4.6% of all cases), were the major causes of AKI in tropical southern Saudi Arabia.

Malaria is rarely reported as a primary cause of AKI in most ME countries, except for Yemen.[21] In the Haja region of northwestern Yemen, malaria caused by *Plasmodium falciparum* was the cause of 27.9% of all cases of AKI. However, prerenal disorders, such as infectious diarrheal diseases, are still the predominant cause of AKI in this region of Yemen because of the climate and poor hygiene. Malarial kidney injury is often a consequence of several hemodynamic, immune, and metabolic disturbances, which may also be accompanied by central nervous system sequelae and by fluid and electrolyte alterations.[22,23] Malarial kidney disease can manifest as AKI in the form of (1) ATN that accompanies or occurs as a complication of severe hemolysis, hemodynamic derangements, and tissue hypoxemia; (2) interstitial nephritis; or (3) glomerular mesangial proliferative lesions with immune complex deposits.[23]

Reporting of the cause of AKI may, however, be biased by the type of referral hospital that documents the various causes. In a retrospective 18-month study from one cancer hospital in the UAE, sepsis and drug-induced nephrotoxicity were the leading causes of AKI because 30% of the patients were immunocompromised and were receiving chemotherapy.[24] In

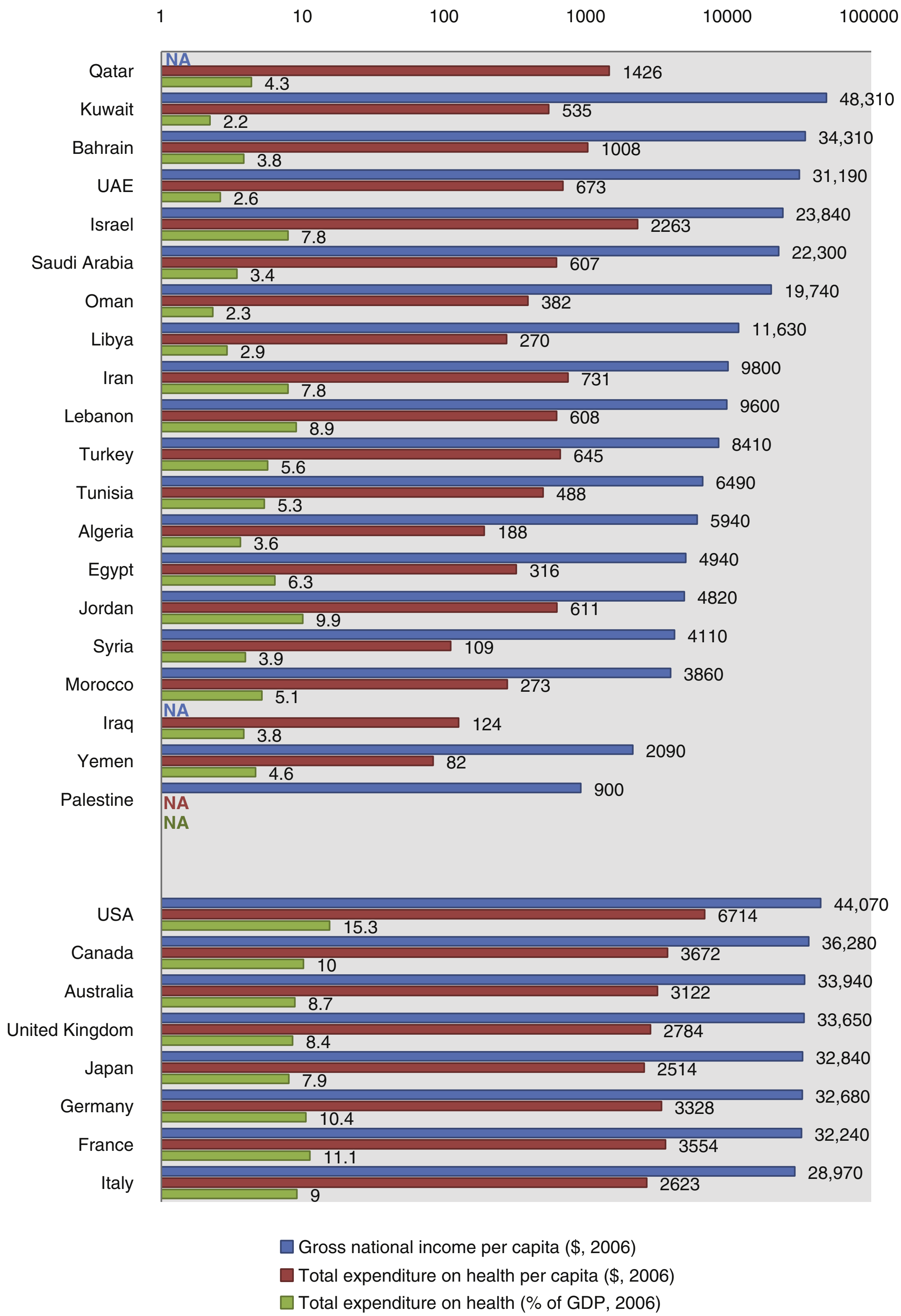


**FIGURE 80-2** Indices of wealth and health care expenditure in the 20 Middle Eastern and selected Western industrialized countries in 2006. For each country, three indices are presented: gross national income per capita, on a purchasing power parity, expressed in international dollars (*blue bars*); total expenditures on health per capita, expressed in international dollars (*red bars*); and total expenditure on health, expressed as percentages of gross domestic product (GDP) (*green bars*). The upper seven countries are the wealthy high-income Middle East (ME) nations. NA, not available; UAE, United Arab Emirates; USA, United States of America. (Data from the World Health Organization: *Countries*. Available at http://www.who.int/countries/en/. Accessed August 2009.)

other reports, preexisting comorbid conditions, such as diabetes, hypertension, and chronic kidney disease (CKD), were documented in approximately one third of all patients with AKI in Jordan and the UAE[16,24] and in as many as 87% of all such patients in Qatar.[20] AKI-associated mortality rates range between 18% and 77% in ME countries.[15-20,24] Al-Homrany[17] reported that uncontrolled sepsis and multiorgan failure were the leading causes of death in southern Saudi Arabia. In his study, mortality was associated with advanced age, oliguria, hospital-acquired AKI, the need for dialysis, and hepatic failure.[17]

Devastating earthquakes have struck some ME countries and are a constant threat because their territory encompasses the Great African Rift Valley. In several publications, investigators have described and analyzed the factors that have had major implications on kidney involvement and outcomes in survivors who sustained crush syndrome in catastrophic earthquakes in Turkey and Iran. Crush syndrome often causes profound hypovolemic shock that (1) is complicated and aggravated by gross disorders of acid-base balance and electrolytes, of which hyperkalemia is life-threatening, and (2) increases susceptibility to myoglobinuric AKI. These complications can occur within hours of the initial injury and can lead to early loss of limb or life.[10,12,25] According to data that was collected after the 1999 Marmara earthquake in Turkey and the 2003 Bam earthquake in Iran, the number of casualties, the incidence of crush injury, and the incidence of myoglobinuric AKI are related to several variables, including the following:

1. The intensity of the earthquake and the magnitude of the aftermath.
2. The time of the day that the earthquake happened: The Turkish earthquake occurred during the night and was associated with more crush injuries than earthquakes that have occurred during the day, because the victims were in the supine position.
3. The population density and type of the residential area at the site of the earthquake: The population density in rural areas, where the buildings are single-storied and made from light construction materials, is less than that in urban areas, where the buildings may be multistoried and made of heavy construction materials.
4. The climate: Earthquake survivors suffer more volume depletion and dehydration in hot weather than in cold weather.
5. The time to rescue, because it reflects both the amount of time under the rubble and the magnitude of imposed pressure in a given time.
6. The extent of destruction of health care facilities at the site of the earthquake and the distance from reference hospitals.
7. The availability of medical support and the availability and efficiency of rescue teams.
8. The availability of renal replacement therapy (RRT).[10,12,26,27]

An important issue in such disasters is the selection of patients with AKI who need early referral to specialized nephrology facilities. Najafi and colleagues[28] developed two decision rules for assessing the absence of risk for AKI by using receiver operating characteristic and linear regression analyses, in order to rationalize prophylactic hydration therapy in crushed earthquake survivors: If the serum creatinine levels are lower than 2 mg/dL, the serum lactate dehydrogenase activity is less than 2000 IU, and the serum uric acid levels are less than 6 mg/dL on day 1, there is almost zero risk for developing AKI. Using a prediction equation derived from multivariable regression analysis,

$$(0.45 \text{ creatine phosphokinase} + 2.5 \text{ lactate dehydrogenase} + 2700 \text{ potassium} + 2000 \text{ uric acid} - 14{,}000) / 10{,}000,$$

they found that the result was most predictive for serum creatinine levels on day 3. The sensitivity and specificity for predicting AKI were 96.6% and 95.7%, respectively, after the result was dichotomized when its value was set at 2.0. However, Ito and Fukagawa[29] commented that the validity of this prediction equation must be confirmed in other disaster settings because the data were collected in a setting that was far from perfect because of the chaos caused by the earthquake.[28]

The ISN's Renal Disaster Relief Task Force has generated systematic help for patients with AKI in disaster-affected areas by gathering information through the use of questionnaires. This information has been used to provide actual help by sending multidisciplinary medical teams and both pharmaceutical and dialysis supplies for on-site treatment of such patients[9-12,26-28] (Table 80-2). Vigorous fluid resuscitation and the use of mannitol are now proven therapies for saving limbs and preventing the development of compartment syndrome in crush injuries, which is the second leading cause of death after disasters. These therapies can also reduce the need to perform fasciotomies, which are associated with severe bleeding, sepsis, and amputations[12,25] (see Table 80-2).

In summary, it is difficult to draw general conclusions about the epidemiology, causes, and outcomes of AKI in many ME countries because of regional variation and methodologic differences in the few studies that have been performed in the region. Well-conducted studies in which the published definition of AKI[30,31] is used are needed to clarify the actual occurrence of AKI. Accordingly, the results of these studies can then be used to identify the needed infrastructure and evaluate treatment strategies in order to improve the clinical outcomes.

## Chronic Kidney Disease

### Epidemiology

The incidence and prevalence of noncommunicable diseases are changing rapidly as a result of demographic transition, and the burden of disease has consequently shifted from the pediatric population to the adult population in many ME countries.[6,32-34] This demographic shift in the burden of disease is exemplified by the emerging epidemic of diabetes mellitus that is occurring globally and affects Arab and Chaldean Americans. In 2007, the International Diabetes Federation (IDF) ranked the UAE (19.5%), Saudi Arabia (16.7%), Bahrain (15.2%), and Kuwait (14.2%) as having the second, third, fourth, and fifth highest estimated prevalence of diabetes mellitus, respectively, in the world.[34a] The IDF also predicts that the prevalence of diabetes mellitus in ME countries, will increase 97%—as opposed to 18% in Europe—by 2025.[35] These alarming statistics for ME countries have been attributed to a combination of increasing urbanization, aging populations, increasing obesity, and falling levels of physical activity.[4,6,32,33,36-38] Accordingly, the direct and indirect medical expenditures that are associated with diabetes mellitus will become a profound economic burden. As a result, ME countries with limited or scarce resources (see

**TABLE 80-2 Crush Syndrome after a Disaster: Steps in Treatment and Local Relief Efforts**

**Major Steps in Treating Patients with the Crush Syndrome**

- Consider the importance of early fluid administration in the field.
  - Initiate an infusion of isotonic saline at the earliest convenience, followed by hypotonic saline-alkaline solution.
  - In patients with adequate urinary flow, add mannitol to the solution.
  - Avoid empirical administration of potassium-containing fluids.
- Closely monitor each patient's fluid intake and urinary output after admission.
  - Administer up to 6 to 12 L of appropriate fluids per day.
  - Remember that in patients with the compartment syndrome and other causes of fluid loss, urinary output may be substantially lower than the amount of administered fluid.
  - Define the amount of fluid to be administered on the basis of the clinical course or central venous pressure measurements.
- Correct electrolyte abnormalities.
  - Hyperkalemia is often fatal and should be corrected vigorously.
  - Hypocalcemia should be corrected only if it causes symptoms.
  - Remember that virtually any other electrolyte disturbance (hyperphosphatemia, hypercalcemia, hypernatremia, hyponatremia, and even hypokalemia) may occur as well and should be treated.
- Consider dialysis as a lifesaving procedure.
  - Begin dialysis when indicated by the presence of any of the following: oliguria or anuria, volume overload, or biochemical abnormalities such as severe uremia, hyperkalemia, and acidemia.
  - Consider the initiation of prophylactic dialysis in patients at high risk for hyperkalemia.
  - In order to estimate logistic needs, remember that the average duration of dialysis will be 13 to 18 days.
  - Consider continuing dialysis support until patients' kidney function has recovered.

**Consecutive Steps for Effective Coordination of Local Relief Efforts**

- Assess the severity of the renal disaster.
  - Estimate the total number of victims, including the number who are or will need to be hospitalized, the number with the crush syndrome, and the number with or at risk for acute renal failure.
- Determine the status of local health care facilities and transportation possibilities.
  - Determine the functional status of local hospitals.
  - Evacuate patients with the crush syndrome from the disaster area.
  - Administer potassium binders, such as sodium polystyrene sulfonate, to patients before they are transported.
- Determine the timing of anticipated hospitalizations and consumption of medical supplies.
  - Discharge victims with mild injuries.
  - Remember that most admissions for the crush syndrome occur during the first week after the disaster and may eventually represent 25% of overall hospitalizations.
  - Use medical equipment economically.
- Prepare schedules for medical and paramedical personnel.
  - Prepare advance global strategies for the allocation of personnel in disaster-prone areas.
  - Assign more experienced personnel during the first days after a disaster.
  - Regulate work hours to reduce stress and avoid burnout of personnel.
  - Remember that for practical or emotional reasons, local personnel may not work as efficiently as usual and may not be able to come to work owing to disaster-related events.
- Estimate the need for renal replacement therapy.
  - Prepare a plan to handle the dialysis program in the event of a disaster.
  - Refer patients with chronic renal failure who require dialysis to outpatient units and temporarily reduce either frequency or duration of dialysis.
  - Define the most appropriate method of dialysis for patients with crush syndrome.
- Deliver medical supplies and personnel.
  - Avoid organizing random support campaigns.
  - Try to ensure the availability of 8-10 sets of dialysis equipment, 4-5 U of blood and blood products, at least 5 L of crystalloids, and 15 g of sodium polystyrene sulfonate (or equivalent) for each potential patient with crush syndrome.

Adapted from Sever MS, Vanholder R, Lameire N: Management of crush-related injuries after disasters, *N Engl J Med* 354:1052-1063, 2006. 

Figure 80-2) will be unable to cope with the social, economic, and public health consequences of complications of diabetes mellitus one of which is CKD.

In addition, the common practice of consanguineous marriages in ME countries has led to a high incidence of genetic disorders, of which some may lead to CKD and end-stage renal disease (ESRD), especially in children, and possibly alter the pattern of renal disease in these countries.[4,39-42] Genetic renal diseases and their complications in the ME are discussed further later in this chapter.

It is difficult to estimate the incidence and prevalence of CKD in most ME countries. Obtaining the epidemiologic statistics concerning CKD, ESRD, and RRT in these countries is a work in progress that is hampered by the lack of well-conducted cross-sectional and longitudinal cohort studies and a lack of reliable registries that incorporate data on comorbid conditions. Hence, the creation of a reliable and easily-accessible medical registry is urgently needed in the ME countries where one is lacking, unreliable, or difficult to access. The information in these registries is essential for planning health policies and the allocation of funds. Community-based screening programs for CKD and risk factors, such as diabetes mellitus, obesity, proteinuria, and hypertension, have been launched in developing countries worldwide under the auspices of the Research and Prevention Committee of the ISN and the Commission for the Global Advancement of Nephrology (COMGAN). This initiative includes ongoing programs in Damanhour, Egypt, and in Khemisset, Morocco.[43] These programs are expected to detect CKD in populations in which the people are unaware of such chronic diseases. It is hoped that the early detection of CKD will increase health awareness and early intervention, which will have an expected effect on disease course, complexity, and costs of overall therapy in comparison with that of late intervention.[43]

Similarly, the International Federation of Kidney Foundations is also attempting to raise awareness by creating educational programs in industrialized and developing countries.[44] Turkey has initiated a surveillance program for determining the prevalence of CKD in adults and children at high risk; as of 2007, Iran and Egypt had not yet started their screening programs.[44] Moreover, many ME countries are involved in the activities of the World Kidney Day initiative of the ISN to enhance public and governmental awareness of the burden of and risk factors for CKD.

The actual or estimated numbers of patients with CKD at each of its stages in each ME country are unclear, according to the classification by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[45] In a 4-year prospective study from a referral center in Kuwait, El-Reshaid and associates[46] reported a high incidence of CKD among Kuwaiti nationals. Specifically, they reported an average annual incidence of 366 per million population, with a higher incidence among the elderly population (aged ≥60 years) of 913 per million population. Of patients with CKD who were admitted to the center, 6% presented with uremic syndrome, and 40% experienced acute deterioration of their kidney function that resulted mainly from drugs (mostly over-the-counter nonsteroidal antiinflammatory drugs), infection, and volume depletion. However, the authors did not report the estimated glomerular filtration rate in their patients. The glomerular filtration rate is important information to include in all future studies because it is a measure of the burden of disease at each stage of CKD. In addition, these values or documentation of proteinuria enables early detection of CKD, which facilitates early intervention and probably improves outcomes.

Although the number of patients who underwent preemptive kidney transplantation might not be included, estimates of the prevalence and incidence of ESRD are more reliable in countries that have a national database in which each patient who has received RRT is registered. The patient numbers in a national registry in ME countries may be underestimated for two additional reasons: (1) The treatment of established ESRD may be beyond the reach of the average citizen in low-income ME countries, such as Yemen, and (2) a high number of expatriates live in some ME countries. Tables 80-3 and 80-4 summarize the available data on ESRD from published articles, registries, and abstracts of proceedings of international symposia in ME countries. Of note, most investigators relied mainly on the results of limited retrospective studies and answers to questionnaires that were sent to leading nephrologists in each country and not on accurate documented statistics, registries, or results of epidemiologic studies.

**TABLE 80-3 Epidemiology of Renal Replacement Therapy in Middle Eastern Countries**

| | Dialysis | | | | Kidney Transplantation | |
|---|---|---|---|---|---|---|
| COUNTRY | FIRST HEMODIALYSIS | NO. OF HEMODIALYSIS CENTERS | INCIDENCE* | PREVALENCE* | DATE OF COUNTRY'S FIRST TRANSPLANTATION | INCIDENCE* |
| Algeria | 1975 | 150 | NA | 330 | 1986 | 0.5 |
| Bahrain | NA | NA | NA | 428 | 1996 | 35 |
| Egypt | 1958 | 300 | NA | 412 | 1976 | 5.2 |
| Iran | 1965 | NA | 63.8 | 357 | 1967 | 26.5 |
| Iraq | 1967 | 27 | NA | 83 | 1973 | NA |
| Israel | 1948 | 67 | 192.4 | 656.5 | 1964 | 22.6 |
| Jordan | NA | 56 | 111 | 420 | 1972 | 15 |
| Kuwait | NA | NA | 72 | 240 | 1979 | 40 |
| Lebanon | NA | NA | 120 | 652 | 1985 | 19 |
| Libya | NA | 40 | NA | 618 | 1988 | 9.3 |
| Morocco | NA | NA | NA | 191 | NA | 0.3 |
| Oman | 1983 | 12 | NA | 189 | 1988 | 2.6 |
| Qatar | 1979 | 5 | 212 | 312 | 1986 | 13 |
| Saudi Arabia | 1971 | 177 | 133 | 498 | 1979 | 19 |
| Syria | NA | 66 | 111 | 228 | 1976 | 18.5 |
| Tunisia | 1967 | 135 | NA | 720 | 1986 | 7 |
| Turkey | 1965 | 796 | 189 | 709 | 1975 | 18.8 |
| United Arab Emirates | 1977 | 6 | NA | 329 | 1985 | NA |
| Yemen | 1978 | 13 | 64 | 91 | 1998 | 1.8 |

*NA,* Not available.

*Per million population.

Data from Abboud[8]; Erek et al[47]; Batieha et al[55]; Saeed et al[194]; Najafi[196]; Al Sayyari[197]; Einollahi[222]; Ehtuish et al[225]; the 2010 report by the Saudi Center for Organ Transplantation[53a]; the 2009 report by the Israeli Center for Disease Control[200a]; the 2007 report by the Turkish Society of Nephrology (http://www.tsn.org.tr/folders/file/registry/registry_2007_tr-en.pdf)[200b]; the 2007 report of the European Renal Association–European Dialysis and Transplantation Association (http://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2007.pdf); and El Matri A: Economic challenge of renal replacement therapy in the Arab world (poster session). Presented at the 2009 World Congress of Nephrology, Satellite Conference: 7th Conference on Kidney Disease in Disadvantaged Populations; Milan, May 26-28, 2009.

Israel and Turkey report their ESRD data to the European Renal Association–European Dialysis and Transplantation Association registry. The registry in Turkey was established in 1990.[47] According to the report published in 2007, the prevalence of ESRD was 578 per million population, and the acceptance rate for new RRT patients was 189 per million population. Of all causes of ESRD in Turkey, the two main contributing causes were diabetic nephropathy and hypertension.[48] The incidence of ESRD in Israel is one of the highest in the world.[49] As in other industrialized countries, the incidence and prevalence of ESRD have increased remarkably in Israel since 1990. The mean prevalence of ESRD was 303 per million population in the period 1989 to 1991, 524 per million population in 1999 to 2001, and 606 per million population in 2003 to 2005; the mean incidence was 99 per million population in 1989 to 1991, 170 per million population in 1999 to 2001, and 179 per million population in 2003 to 2005. The average annual increase in incidence rates between 1989 and 2005 was 4.2%; this increase was positively associated with age, inasmuch as the incidence increased mainly in the elderly population (aged ≥65 years).

In 2001, diabetes mellitus accounted for 41% of the newly diagnosed cases in patients who underwent RRT, as opposed to 19% who started RRT in 1989. As expected, the survival rates of patients with diabetes mellitus are lower than those of patients without diabetes mellitus. However, the escalating trend has not been consistent: The increase in the average annual incidence of ESRD was 8.1% between 1994 and 1999, in comparison with 0.4% between 2000 and 2005. Calderon-Margalit and associates[49] offered various explanations for this discrepancy, but none was able to account for it completely. They suggested that the difference could be attributed to an increase in the incidence of diabetes mellitus in the population and to substantial demographic changes in the Israeli population that occurred during the 1990s as a result of the massive immigration from the former Soviet Union, inasmuch as many of these immigrants suffered from chronic diseases. Data from the report of the Israeli Center for Disease Control (ICDC) indicated that the incidence of ESRD stabilized in the period 2006 to 2007 at 192 per million population, but the prevalence was still high in 2007 at 1048 per million population (669 patients undergoing dialysis per million population, 379 kidney transplant recipients per million population).

**TABLE 80-4 Modalities of Renal Replacement Therapy for Treating End-Stage Renal Disease in Selected Middle Eastern Countries**

| COUNTRY | TRANSPLANTATION (%) | PERITONEAL DIALYSIS (%) | HEMODIALYSIS (%) |
|---|---|---|---|
| Iran | 48.8 | 3.5 | 47.7 |
| Israel | 36.2 | 6.2 | 57.6 |
| Jordan | 13.9 | 2.4 | 83.6 |
| Kuwait | 5 | 12.5 | 82.5 |
| Lebanon | 27 | 2.7 | 70.3 |
| Oman | 39.1 | 1.8 | 59.1 |
| Qatar | 48.4 | 6.5 | 45.2 |
| Saudi Arabia | 39 | 5.8 | 55.2 |
| Turkey | 11.2 | 10.6 | 78.2 |
| United Arab Emirates | 34.2 | 4.6 | 61.2 |

Percentages are the proportions of the total population of patients with end-stage renal disease in each country.

Data from Abboud[8]; Erek et al[47]; Batieha et al[55]; Saeed et al[194]; Najafi[196]; Al Sayyari[197]; Einollahi[222]; Ehtuish et al[225]; the 2010 report by the Saudi Center for Organ Transplantation[53a]; the 2009 report by the Israeli Center for Disease Control[200a]; the 2007 report by the Turkish Society of Nephrology[200b]; and the 2007 report by the European Renal Association–European Dialysis and Transplantation Association report (http://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2007.pdf).

The Tunisian registry was started in 1990, and its trends in ESRD are similar to those in Israel: The incidence and prevalence of ESRD in Tunisia are also increasing.[50] The incidence of ESRD increased from 81.6 per million population in the period 1992 to 1993 to 158.8 per million population in 2000 to 2001; the average annual increase was 9.6%. The incidence of ESRD in elderly persons, women, and individuals with diabetic nephropathy has risen steeply. However, regional variations were noted among urban and rural districts.[50,51]

Abboud[8] reviewed the status of ESRD and its therapy in 10 ME countries: Yemen, the six gulf countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the UAE), Syria, Jordan, and Lebanon. He reported that the estimated average incidence of ESRD in these countries was 93 per million population (the lowest was 64 per million population in Yemen, and the highest was 212 per million population in Qatar), and the average prevalence was 352 per million population (the lowest was 80 per million population in Kuwait, and the highest was 462 per million population in Saudi Arabia). A treatment program for established ESRD in Iran was introduced in 1975. The reported number of Iranians with ESRD has also increased, and this increase is mirrored in the growing number of dialysis centers and renal transplantation programs. The incidence and prevalence of ESRD were 49.9 per million population and 238 per million population, respectively, in 2000 and increased to 63.8 per million population and 357 per million population, respectively, in 2006.[52,53]

The Saudi Center for Organ Transplantation (SCOT) has established an open-access RRT registry that provides annual information on the epidemiologic statistics and treatment of ESRD, in Saudi Arabia. In 2010, the center reported that the incidence of hemodialysis was 133 per million population, with a prevalence of 498 per million population and an average annual increase of 7.9%.[53a]

In the ME countries for which detailed statistics on the epidemiologic statistics and treatment of ESRD are available, there is a male predominance among patients with ESRD, which is concordant with the reported male predominance among patients with ESRD worldwide.[54] The mean age of patients undergoing dialysis in each ME country varies between 42 and 65 years. Interestingly, the youngest patients with ESRD on dialysis are in the developing ME countries, and the oldest patients with ESRD on dialysis are in Israel.[48,49,52,55-57] Of note, kidney diseases and risk factors or therapy in expatriates—who may make up as much as 50% of the population, especially in the wealthy Gulf countries—have not been carefully investigated. This population needs to be distinguished from the resident population and may require special attention because of their different ethnic, socioeconomic, and environmental backgrounds.[8,52,58]

## Causes of Chronic Kidney Disease

The causes of CKD in ME countries are highly influenced by the bioecology of a particular region, and the ethnic and socioeconomic background of its population. Accordingly, the various causes of CKD are ranked differently in ME countries. The populations of the five ME countries in North Africa—Morocco, Algeria, Tunisia, Libya, and Egypt—have similar ethnicity and socioeconomic backgrounds, in that they are of African descent that has been intermixed with Berber, Arab, and Mediterranean population streams.[59] In this region, interstitial nephritis and glomerulonephritis each account for about 20% of all cases of CKD.[59] The number of individuals with interstitial nephritis increased during the 2000s, possibly as a result of environmental pollution and abuse of over-the-counter drugs.[60] Most cases of glomerulonephritis are of the proliferative type, whereas immunoglobulin A (IgA) nephropathy is rare. The underlying reason for high prevalence of proliferative glomerulonephritis in these ME countries is that it reflects postinfectious renal disease caused by viruses, bacteria, and parasites. Although the number of individuals with diabetes mellitus is increasing in most other ME countries, diabetes mellitus and diabetic nephropathy account for only 5% to 20% of all causes of ESRD in the five North African countries. In Egypt, Libya, and southern Algeria, about 7% of patients with CKD suffer from obstructive uropathy as a result of urinary schistosomiasis caused by *Schistosoma haematobium* or *Schistosoma mansoni*.

In a prospective study of Kuwaiti nationals with CKD, El-Reshaid and associates[46] reported that the most common cause of CKD was glomerulonephritis (32%), followed by diabetic nephropathy (24%) and interstitial nephritis (11%). They also reported that focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy were the most prevalent lesions among patients with primary glomerulonephritis. With regard to all causes of ESRD in ME countries, Syria, Jordan, Lebanon, Israel, Turkey, Iran, and the six Gulf countries still report diabetes mellitus as the most frequent cause of ESRD (20% to 40%), followed by hypertension (11% to 30%), and glomerulonephritis (11% to 24%).[8,48,49,52,55] It is noteworthy that tuberculosis, other bacterial infections, and familial Mediterranean fever (FMF) are the main causes of renal (type AA) amyloidosis in many ME countries.[59,61]

## Genetic Disorders

Genetic kidney diseases have received much attention in pediatric and adult nephrology because the underlying molecular defects in many of these diseases have been elucidated, as a result of advances in genetics and molecular biology. The ME population is ethnically and genetically diverse.[62] The primary demographic features of Arab Muslim and Druze communities in the ME include large families, rapid population growth, and high rates of consanguinity. Among Palestinian Arabs, more than 40% of marriages are between relatives, and of these, 50% are between first cousins.[62,63] In Bedouin society, 40% of women of childbearing age are married to first cousins.[64] In contrast, the consanguinity rate among Israeli Jews is reported to be 2.3%, and of these, first-cousin marriages account for 0.8%. The highest consanguinity rate among Israeli Jews (7.1%) is found among Eastern (i.e., Oriental non-Sephardic) Jews.[65]

High consanguinity rates have been reported in the Saudi Arabian, Kuwaiti, Lebanese, and Moroccan populations.[4,39-42,66-68] The results of an epidemiologic survey from Lebanon revealed that 26% of patients receiving chronic hemodialysis were the children of consanguineous parents.[39] In addition, Barbari and colleagues[39] reported that the risk for a family history of kidney disease was particularly high among patients from consanguineous families who were receiving hemodialysis.[39] Populations with a high rate of consanguinity also have an increased prevalence of adulthood diseases that are associated with renal insufficiency, such as hypertension, metabolic syndrome, and diabetes mellitus.[69,70] A significant proportion of genetic kidney diseases are inherited in an autosomal recessive manner. It is therefore not surprising that these diseases occur most frequently in communities with high consanguinity rates.[71]

Consanguineous populations are not expected to have a different mutation rate. Consanguinity, however, may enhance allelic and locus heterogeneity.[69-72] Seventy-one different autosomal recessive kidney diseases were reported in Palestinian Arabs (reviewed by Zlotogora[63]); these include primary renal diseases (congenital nephritic syndrome and nephronophthisis), metabolic and tubular defects (cystinuria, Bartter's syndrome, renal tubular acidosis, and oxalosis), and FMF (discussed in detail later in this chapter). The influence of genetic factors is very evident in pediatric patients with kidney diseases, particularly in Saudi Arabia and Syria where increased numbers of congenital and hereditary kidney and urologic diseases are now being reported.[62,73] The results of an extensive study of both Jewish and Bedouin populations of southern Israel showed that genetic kidney diseases are over-represented in the pediatric population (Table 80-5).[41]

### Genetic Glomerular Diseases

A substantial number of patients in the ME with renal disease have familial glomerular diseases whose spectrum includes familial hematuria, Alport's syndrome, IgA nephropathy, and familial focal glomerulosclerosis.[41,74,75] A recessive form of steroid-resistant nephrotic syndrome has been shown to be associated with mutations in the *NPHS2* gene, which encodes the glomerular protein podocin.[76] The most common phenotype is of a nephrotic syndrome that is resistant to immunosuppressive treatment in early childhood, and most patients with this disease develop ESRD after 5 to 20 years. In a group of children from two consanguineous families of Israeli-Arab descent, mutation analysis of the *NPHS2* gene revealed homozygosity for the C412T nonsense mutation (R138X).[77] The same mutation was also found in Israeli-Arab patients with nonfamilial steroid-resistant nephrotic syndrome but not in Jewish children or in children from both ethnic groups with steroid-sensitive nephrotic syndrome.[77] Interestingly, cardiac anomalies, especially left ventricular hypertrophy, pulmonary stenosis, and discrete subaortic stenosis, were detected in a high proportion of the children with *NPHS2* mutations.[78] Frishberg and associates[78] speculated that podocin may have a role in normal cardiac development because podocin messenger RNA is reported to be expressed in the human fetal heart.

At least 53 *NPHS2* mutations have also been found in Turkish children with familial and sporadic steroid-resistant nephrotic syndrome.[75,79] Among Turkish patients with these mutations, the proportion of patients with kidney failure or

**TABLE 80-5 Summary of Genetic Kidney Diseases in Southern Israel, 1994 to 2005**

| TYPE OF DISEASE | DISEASE | OMIM NO. | NO. OF PATIENTS | NO. OF FAMILIES | NO. OF BEDOUIN PATIENTS | NO. OF JEWISH PATIENTS | OUTCOME | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | ALIVE | CKD | TRANSPLANTATION | DEATH |
| Glomerular | Alport's syndrome | 301050 | 5 | 2 | 0 | 5 | 3 | 1 | 1 | |
| | Benign familial hematuria | 141200 | 1 | 1 | 0 | 1 | 1 | | | |
| Tubular | Cystinuria | 220100 | 10 | 7 | 10 | 0 | 10 | | | |
| | Distal RTA | 602722 | 4 | 3 | 2 | 2 | 4 | | | |
| | Nephrogenic diabetes insipidus | 125800 | 15 | 11 | 14 | 1 | 15 | | | |
| | Type II Bartter's syndrome | 241200 | 9 | 5 | 2 | 6 | 8 | | | 1 |
| | Type IV Bartter's syndrome | 602522 | 16 | 9 | 16 | 0 | 14 | | | 2 |
| | Unclassified Bartter's syndrome | | 2 | 2 | 1 | 1 | 2 | | | |
| | Familial hypomagnesemia | 602014 | 15 | 7 | 15 | 0 | 15 | | | |
| | Gitelman's syndrome | 263800 | 3 | 3 | 1 | 2 | 3 | | | |
| | Hypophosphatemic rickets | 307800 | 4 | 2 | 3 | 1 | 4 | | | |
| Cystic/NPHP | ADPKD | 173900 | 10 | 9 | 0 | 10 | 10 | | | |
| | ARPKD | 263200 | 13 | 10 | 12 | 1 | 3 | 6 | | 4 |
| | Bardet-Biedl syndrome | 209900 | 3 | 2 | 3 | 0 | 2 | 1 | | |
| | Juvenile nephronophthisis | 256100 | 2 | 2 | 1 | 1 | | 2 | | |
| | Infantile nephronophthisis | 602088 | 3 | 3 | 3 | 0 | | | 2 | 1 |
| Metabolic | Fanconi-Bickel syndrome | 227810 | 2 | 2 | 2 | 0 | 2 | | | |
| | Xanthinuria | 278300 | 5 | 2 | 5 | 0 | 5 | | | |
| | Lowe's syndrome | 309000 | 1 | 1 | 0 | 1 | | | | 1 |
| | Cystinosis | 219800 | 2 | 2 | 0 | 2 | 1 | | 1 | |
| Other | Atypical HUS | 134370 | 8 | 4 | 8 | 0 | 4 | 1 | | 3 |
| | Renal tubular dysgenesis | 267430 | 4 | 4 | 4 | 0 | | | | 4 |
| Total | | | 137 | 93 | 102 | 34 | 106 | 11 | 4 | 16 |

*ADPKD,* Autosomal dominant polycystic kidney disease; *ARPKD,* autosomal recessive polycystic kidney disease; *CKD,* chronic kidney disease; *HUS,* hemolytic uremic syndrome; *NPHP,* nephronophthisis; *OMIM,* Online Mendelian Inheritance in Man catalog (http://www.ncbi.nlm.nih.gov/OMIM); *RTA,* renal tubular acidosis.

Modified from Finer G, Shalev H, Landau D: Genetic kidney diseases in the pediatric population of southern Israel, *Pediatr Nephrol* 12:910-916, 2006.

ESRD, or both, was significantly higher (19 of 73) than that of patients without these mutations (28 of 222). Furthermore, the mean time for progression to renal failure was significantly shorter in patients with these mutations than in those without these mutations.[75]

The *NPHS1* gene encodes nephrin, an essential protein for maintaining the normal structure and function of the slit diaphragm of the visceral glomerular epithelial cell. Three mutations in the *NPHS1* gene were reported in 12 children with congenital nephrotic syndrome from a large consanguineous Israeli Arab family.[72] Steroid-sensitive nephrotic syndrome is rarely reported to have a familial pattern. However, a familial pattern associated with this condition has been reported in Israeli Bedouin families with a high rate of consanguinity, and the authors of the report proposed that the increased incidence of steroid-sensitive nephrotic syndrome resulted from selective enrichment of susceptibility genes in this population.[80]

## Genetic Metabolic Diseases and Inherited Tubular Disorders

Primary hyperoxaluria type I and type II are relatively rare autosomal recessive inborn errors of glyoxylate metabolism. Types I and II are characterized by overproduction of oxalate by the liver, and type II, by oxalate overproduction by other tissues.[81] The more frequent primary hyperoxaluria type I (Online Mendelian Inheritance in Man [OMIM] catalog number 604285) is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. Primary hyperoxaluria type II (OMIM numbers 260000 and 604296) is caused by a deficiency of the cytosolic enzyme glyoxylate reductase (glyoxylate hydroxypyruvate reductase), which catalyzes the reduction of glyoxylate and hydroxypyruvate. When AGT activity is absent, glyoxylate is converted to oxalate, which forms insoluble calcium oxalate, which in turn is deposited in the kidneys and causes progressive renal insufficiency (nephrolithiasis, nephrocalcinosis, and progressive inflammation with interstitial fibrosis). Deposition of calcium oxalate also occurs in extrarenal tissues, including the retina, myocardium, blood vessels, bone, and central nervous system.[81]

Cases of primary hyperoxaluria type I and isolated cases of type II have been reported in Israeli families, especially in Israeli-Arab families, in 22 of which at least 15 different mutations in the AGT-encoding *AGXT* gene have been detected.[82-84] Marked intrafamilial phenotypic heterogeneity with no definite genotype-phenotype correlation was noted in these families, and the prevalent phenotype was one of early onset of disease with progression to ESRD in the first decade of life.[83] Primary hyperoxaluria is a common cause of nephrolithiasis, nephrocalcinosis, and kidney failure in children from the ME countries in western North Africa, from Saudi Arabia, and from Kuwait. [59,85,86] Primary hyperoxaluria is probably underdiagnosed because by the time of diagnosis, advanced kidney failure has usually developed, or it is diagnosed on biopsy of kidney transplant recipients with early graft dysfunction resulting from oxalate deposition.[81]

Cystinuria is another common cause of nephrolithiasis in various ethnic groups in ME countries.[59,86,87] This autosomal recessive kidney disease is caused by a mutation in either one or both of two genes: the *SLC3A1* gene on chromosome 2p16.3, which encodes the solute carrier family 3 (cystine, dibasic, and neutral amino acid transporters), member 1 (also known as rBAT, $ab^{o,+}$, AT transporter related protein); and the *SLC7A9* gene on chromosome 19q13.1, which encodes the solute carrier family 7 (cationic amino acid transporter, y+ system), member 9 (also known as BAT1, $b^{o,+}$, AD transporter protein). The disease manifestations caused by either mutation are similar.[88,89] Mutations in SCL3A1 have been detected in Turks, Muslim Arabs, Druze, and Ashkenazi and Sephardic Jews of Persian and Yemenite origin. The disease is also common among Libyan Jews, among whom the estimated prevalence is 1 per 2500 and the carrier rate is 1 per 25. In this population, the disease is caused by a single founder mutation, V170M, in the *SLC7A9* gene.[88-92]

Fabry's disease is a rare X-linked sphingolipidosis caused by deficiency of α-galactosidase A (ceramide trihexosidase). A mutation in the gene that encodes this enzyme results in insufficient breakdown of lipids, which then progressively accumulate to harmful levels in the eyes, kidneys, autonomic nervous system, and cardiovascular system. In untreated patients, the accumulation of globotriaosylceramidase in lysosomes may result in multiple organ damage that includes the development of ESRD between the fourth and fifth decades of life. Histologic evidence of Fabry's disease has been detected in graft biopsy samples many years after successful kidney transplantation.[93,94] Although most disease features have been reported in adults, a pediatric disease phenotype that includes acroparesthesia, skin manifestations, and glomerular alterations has been described.[94,95] Fabry's disease has been diagnosed in families in Israel and Turkey.[93-96] However, Fabry's disease is probably underdiagnosed in other ME countries because of limited screening or awareness.

Bartter's syndrome and Gitelman's syndrome belong to a group of inherited salt-losing tubulopathies with distinct phenotypes; they are caused by an inherited defect in ion transporters in the loop of Henle and distal convoluted tubule, respectively. Most cases of the variants of Bartter's syndrome in the ME are reported in Israeli Arabs, in large Bedouin communities living in southern and northern Israel, and in Kuwaiti children.[41,97,98] Some rare genetic kidney diseases that have reported in ME communities are listed in Table 80-6.[99-107] Other genetic diseases may cause glomerular and various tubulointerstitial complications; an example is sickle cell anemia, a hemoglobinopathy that is prevalent in the ME countries in western North Africa and the Arabian peninsula.[59,62,108-110]

## Familial Mediterranean Fever

FMF is the most common of the hereditary periodic fever syndromes and probably the most common genetic disease in the ME. FMF is an autoinflammatory autosomal recessive inherited disease that is characterized by recurrent attacks of fever, serositis, arthritis, and erysipelas-like skin lesions. The disease affects several ethnic groups in the ME, including Sephardic Jews, Armenians, Turks, and Arabs.[111] The most significant complication of FMF is renal amyloidosis that progresses to nephrotic syndrome and renal insufficiency. Renal amyloidosis is occasionally diagnosed in patients without a typical history of FMF attacks.

In the 1990s, two groups identified the *MEFV* gene by positional cloning as the underlying genetic cause of FMF.[112,113] At least 208 mutations in the *MEFV* gene have

**TABLE 80-6 Rare Genetic Diseases with Renal Involvement Reported in Middle Eastern Communities**

| COUNTRY/ COMMUNITY | DISEASE | OMIM NO. | PHENOTYPE | DEFECT/MUTATION | REFERENCES |
|---|---|---|---|---|---|
| Saudi Arabs, Turks | Alström's syndrome* | 203800 | Retinal degeneration, obesity, cardiomyopathy, sensorineural hearing loss, insulin resistance, renal impairment | *ALMS1* gene ubiquitously expressed, encodes a protein of unknown function | 99, 107 |
| Israeli Arabs | Idiopathic renal hypouricemia | 606142 | Increased renal clearance of uric acid, hypouricemia, nephrolithiasis, exercise-induced acute renal failure | *SLC2A9* gene, encodes glucose transporter 9 (GLUT9) | 100, 104 |
| Israeli Jews, Turks | Dent's disease* | 300009 | Low-molecular weight proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, rickets, renal failure, hypokalemic metabolic alkalosis | *CLCN5*, the chloride/proton CIC-5 antiporter gene | 101, 103 |
| Israeli Arabs | Familial renal glycosuria and aminoaciduria† | 233100 and 183381 | Glycosuria, aminoaciduria | *SLC5A2*, the kidney-specific $Na^+$/glucose cotransporter gene | 106 |
| Israeli Jews | Proximal renal tubular acidosis and glaucoma | 604278 and 603345 | Short stature, deformed teeth, bilateral glaucoma, blindness, metabolic acidosis | *SLC4A4*, the sodium bicarbonate cotransporter (NBCe1) gene | 102 |
| Iranians | Familial lecithin-cholesterol acyltransferase deficiency‡ | 245900 | Lower extremity edema, proteinuria, corneal opacities, hypercholesterolemia, hemolytic anemia | Lecithin-cholesterol acyltransferase *(LCAT)* gene | 105 |

*X-linked.
†Autosomal recessive.
‡Diagnosis made on the basis of familial history and electron microscopic findings on kidney biopsy.
*OMIM*, Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/OMIM) catalog.

been reported, and more than 91 of these mutations have been found to be associated with FMF.[113a] The *MEFV* gene encodes the protein pyrin (or marenostrin). The gene is located on the short arm of chromosome 16 (16p13.3) and includes 10 exons that encode 781 amino acids. The *MEFV* gene is expressed predominantly in polymorphonuclear cells (PMNCs), eosinophils, and monocytes but not in lymphocytes. It is also expressed in dendritic cells and fibroblasts from the synovium, peritoneum, and skin.[114,115] Pyrin is thought to be involved in the regulation of cellular processes that are associated with the synthesis, processing, and release of inflammatory proteins by PMNCs and with cell death.[116]

The carrier frequency of mutant alleles is high, as much as 1:3 to 1:5 in certain populations in ME countries (Armenians, Jews, and Turks), and the most common reported mutations are in M694V, V726A, M680I, M694I in exon 10, and E148Q in exon 2.[117,118] The most frequent *MEFV* mutations in the ME populations are listed in Table 80-7.[119-137] Mutations in the *MEFV* gene have also been reported in Spanish, Italian, Greek, Portuguese, Indian, Chinese, and Japanese populations.[138,139] Most *MEFV* mutations are single–amino acid substitutions (missense), and many patients with FMF have a single *MEFV* mutation.

The clinical spectrum of FMF and the elucidation of the molecular biology, structure, and regulation of pyrin and its role during inflammation have been reviewed.[116,140,141] Five different domains have been identified within pyrin: a PYRIN domain, a bZIP transcription factor basic domain, a B-box zinc finger domain, an α-helical (coiled-coil) domain, and a B30.2 domain (Figure 80-3). Each domain has a distinct role in protein-protein interactions during inflammation that results in cytokine activation, transcriptional regulation, cytoskeleton signaling, and apoptosis. The PYRIN domain had been found in more than 20 inflammatory and apoptotic proteins. Through homotypic domain interactions, the PYRIN domain can bind to the common adaptor apoptosis–associated specklike protein (ASC), which has an N-terminal PYRIN domain and a C-terminal CARD domain, participates in the proteolytic activation of caspase-1 in cytoplasmic protein complexes (inflammosomes), and regulates the maturation and secretion of the proinflammatory cytokines interleukin (IL)–1β, IL-18, and IL-33.[142] Inflammasomes contain members of the nucleotide-binding oligomerization domain, leucine-rich repeat, and PYRIN domain–containing subfamily of proteins, now known as NLRP proteins. Mutations in the gene expression of the NLRP protein NRLP3 (cryopyrin) are associated with dominantly inherited or de novo autoinflammatory diseases, such as cryopathies or cryopyrin-associated periodic syndromes.[143]

The presence of the bZIP transcription factor basic domain, the B-box zinc finger domain, and two universal nuclear localization signals in the N-terminal of pyrin suggests that pyrin may act as a nuclear factor. Several studies have shown that pyrin is cleaved by caspase-1, and the N-terminal cleaved fragment (330 amino acids) localizes to the nucleus and potentiates activation of nuclear factor κ light-chain enhancer of activated B cells (NF-κB).[144] The N-terminal of pyrin is also needed for pyrin to bind to the microtubules. The three serine residues 208, 209, and 242 that are located between the PYRIN and bZIP domains are critical for the interactions with 14.3.3 proteins, which are potent antiapoptotic factors and play an important role in the subcellular compartmentalization of pyrin.[145]

The effects of pyrin on IL-1β are complex. Pyrin competitively binds with the ASC adaptor protein through the PYRIN domain (see Figure 80-3), an action that prevents

**TABLE 80-7 Genotype-Phenotype Correlations in Several Patient Populations with Familial Mediterranean Fever**

| POPULATION/ COMMUNITY | FREQUENT MUTATIONS | PHENOTYPE | AMYLOIDOSIS (% PATIENTS) | ASSOCIATED SYNDROMES AND DISEASES | REFERENCE |
|---|---|---|---|---|---|
| Israeli Jews and Arabs | M680I, M694V, M694I, V726A | Arthritis, fever, serositis, vasculitis | 1.4% (Associated with mutation in M694V) | NR | Brik et al[124] |
| Israeli Jews and Arabs | M694V (very common in Jews), M694I (exclusive in Arabs), M680I,V726A, E148Q | Arthritis, fever, serositis, vasculitis | NR | NR | Ben-Chetrit et al[123] |
| Israeli Arabs | M694V (associated with severe disease), V726A (most common) | Arthritis, fever, serositis, vasculitis | NR | NR | Shinawi et al[134] |
| Israeli Jews of North African origin and Arabs* | M694I, M694V (very common in North African Jews) E148Q | Synovitis, pleuritis, abdominal pain, skin rash | 95%* | Focal glomerulosclerosis | Ben-Chetrit and Backen-roth[122] |
| Israeli Jews of North African origin, Ashkenazi Jews, Jews of Iraqi origin, Israeli Arabs, and Druze | E148Q M694V(very common in North African Jews) V726A | FMF criteria[128] | 4.6% (most common in M694V homo-zygous) | NR | Zaks et al[137] |
| Turks | M680I, M694V, M694I, V726A, E148Q | Abdominal pain, fever, arthralgia, chest pain, skin rash | 3% (Mostly associ-ated with M694V) | NR | Solak et al[135] |
| Turks | M680I, M694V, V726A | Abdominal pain, fever, arthralgia, pleuritis, muscle pain, skin rash | 12.9%; 0.9% as the main disease mani-festation (phenotype II, associated with M694V) | Nonamyloid renal disease, Henoch-Schönlein purpura, polyarteritis nodosa, Behçet's syndrome, rheumatic fever, uve-itis, inflammatory bowel disease | Tunca et al[136] |
| Jordanian Arabs Palestinian Arabs | M680I, M694V, M694I, V726A, E148Q | Abdominal pain, fever, arthralgia, myalgia, skin rash | 1% (associated with M694V) | Protracted fever myalgia syndrome; 42% homozygous for M694V | Langevitz et al[127], Majeed et al[129] |
| Jordanian Arabs | M680I, M694V, V726A, E148Q | Abdominal pain, fever, arthralgia | 9% (M694V in 1 patient, V726A/ M680I in 2 patients) | Celiac disease, folliculitis | Medlej-Hashim et al[131] |
| Palestinian Arabs | M680I, M694V, V726A, E148Q | NR | NR | NR | Ayesh et al[120] |
| Arabs from Jordan, Egypt, Syria, Iraq, and Saudi Arabia | M694V, V726A, E148Q | NR | NR | NR | Al-Alami et al[119] |
| Iranian Azeris who live in Turkey | M680I, M694V, M694I, V726A, E148Q | Abdominal pain, fever, arthralgia, pleuritis, skin rash | 7% | NR | Esmaeili et al[126] |
| Egyptian Arabs | M680I, M694V, V726A | Abdominal pain, chest pain, fever, arthritis, myalgia | NR | NR | Settin et al[133] |
| Syrian Arabs | M680I, M694V, M694I, V726A, E148Q, A744S, R761H | Serositis, fever, arthritis, pleuritis | 5% | NR | Mattit et al[130] |
| Lebanese Arabs | M680I, M694V (very frequent), M694I, V726A, E148Q (very frequent); minor alleles also detected | Serositis, fever, arthritis, chest pain | NR | NR | Sabbagh et al[132] |
| Algerian, Moroccan, and Tunisian Arabs | M694V and M694I (most common), M680l, M680I, A744S, V726A, E148Q | Serositis, fever, arthritis, chest pain | NR | NR | Belmahi et al[121] |
| Tunisian Arabs | M680I (most common), M694V, M694I, V726A, E148Q, A744S, R761H, 1692del | FMF criteria[128] | 3.5% | NR | Chaabouni et al[125] |

*Study performed in patients with end-stage renal disease.
*FMF,* Familial Mediterranean fever; *NR,* not reported.

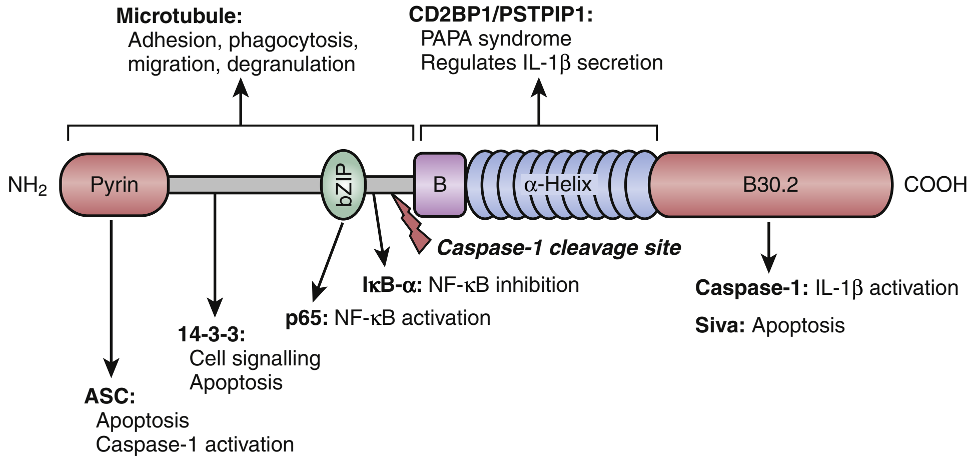


**FIGURE 80-3** The structure of pyrin and its interacting proteins. Pyrin comprises five domains, each of which has specific protein-protein interactions: a PYRIN domain, a bZIP transcription factor basic domain, a B-box zinc finger domain, an α-helical (coiled-coil) domain, and a B30.2 domain. The entire N-terminal of pyrin is necessary to bind pyrin to microtubules, and three serine residues, which are located between the PYRIN and the bZIP domains, are essential for the 14.3.3 protein–PYRIN interaction. The PYRIN domain interacts with common adaptor apoptosis–associated specklike protein (ASC); the bZIP basic domain and adjacent sequences interact with p65 and IκB kinase α (IκBα); the B-box zinc finger and α-helical (coiled-coil) domain interact with PAPA protein (PSRPIP1), which is also known as CD2BP1; and the B30.2 domain interacts with caspase-1.The caspase-1–mediated cleavage site of pyrin is located between the bZIP basic domain and the B-box zinc finger domain. (Adapted from Chae JJ, Aksentijevich I, Kramer DL: Advances in understanding of familial Mediterranean fever and possibilities for targeted therapy, *Br J Haematol* 146:467-478, 2009.)

ASC binding to caspase-1 and the formation of the inflammasome. Pyrin also binds to caspase-1 through the B30.2 domain. The overall result of these two actions is suppression of IL-1β release. Under certain circumstances, however, pyrin's interaction with ASC adaptor protein modulates the arrangement of pyroptosome, a protein that activates caspase-1 and promotes the release of IL-1β.[146] The B30.2 domain of pyrin is the target of most *MEFV* mutations. This domain, which is located at the C-terminal domain of the protein, is a site of ligand binding and signal transduction. Thus mutations in the B30.2 domain may lead to an excessive inflammatory response as a result of the decreased ability of pyrin to control IL-1β activation.

The putative role of pyrin in the pathogenesis of FMF is depicted in Figure 80-4. According to this model, the active caspase-1 subunits p10 and p20 are produced in the inflammasome by inducing proximity-mediated autocatalysis. The wild-type B30.2 domain of pyrin interacts with the p20 and p10 subunits and consequently prevents the formation of an active p20/p10 heterodimer. In FMF, FMF-associated pyrin B30.2 mutants interact with the p20 and p10 subunits but to a lesser extent than does the wild-type B30.2 domain, therefore enabling assembly of the p20/p10 heterodimer, activation of IL-1β, and the induction of inflammation. The active p20/p10 heterodimer then cleaves pyrin at Asp330, which is located between the bZIP basic domain and the B-box zinc finger domain. The N-terminal cleaved fragment then interacts with the p65 subunit of NF-κB and the inhibitor protein IκB kinase α through the bZIP basic domain and adjacent sequences in order to activate NF-κB and induce the expression of inflammatory genes.[116]

### Clinical Spectrum and Renal Disease

The wide clinical spectrum and the genotype-phenotype correlations in FMF are influenced by genotype (extent and position of the *MEFV* mutation), ethnicity, and environmental factors. In Arab patients with FMF, the worst disease severity is associated with alleles carrying the mutations M694V/M694V and M694V/M726A, whereas the M694I/ M694I mutation is associated with a mild form of the disease.[147] In Turkish patients with FMF, the common M694V mutation is associated with more severe disease but not with amyloidosis.[136,141] In contrast, the homozygous *M694V* mutation was reported to be associated with amyloidosis in Jews from North Africa, in Arabs, in Turks, and also with the protracted febrile myalgia syndrome, which is a type of myalgia that is associated with FMF in Arabs.[123,124,129,131,136,137,147]

FMF has traditionally been considered an autosomal recessive genetic disease. As many as 25% of patients with clinical FMF have only one *MEFV* mutation.[135,136,140] This finding could explain the vertical transmission of the disease in some families. In patients with FMF who have a single *MEFV* mutation, an additional but less common mutation may be account for the disease, but this has not yet been confirmed in carefully performed studies. One possible mechanism to explain the occurrence of the disease in such cases would be the combination of the single *MEFV* mutation with one or more polymorphisms of the genes that encode inflammatory proteins, such as those of the IL-1β signaling pathway or the proteins that are associated with pyrin function. The impact of *MEFV* mutations has been shown in other inflammatory diseases, such as Henoch-Schönlein purpura, polyarteritis nodosa, Behçet's disease, rheumatic heart disease, and rheumatoid arthritis (reviewed by Guz and associates[141]). Of interest is that individuals who carry a single mutated *MEFV* allele can also suffer from the syndrome of periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA); ankylosing spondylitis; and Crohn's disease.[148]

Secondary or reactive AA amyloidosis is the most severe complication of FMF. Before the advent of colchicine treatment, amyloidosis was reported to occur in about 75% of patients with FMF who were older than 40 years.[149] The disease is caused by the extracellular deposition of amyloid A fibrils. These fibrils consist of β-pleated sheet polymers of the N-terminal fragments, the products of incomplete proteolytic digestion of the acute-phase precursor serum

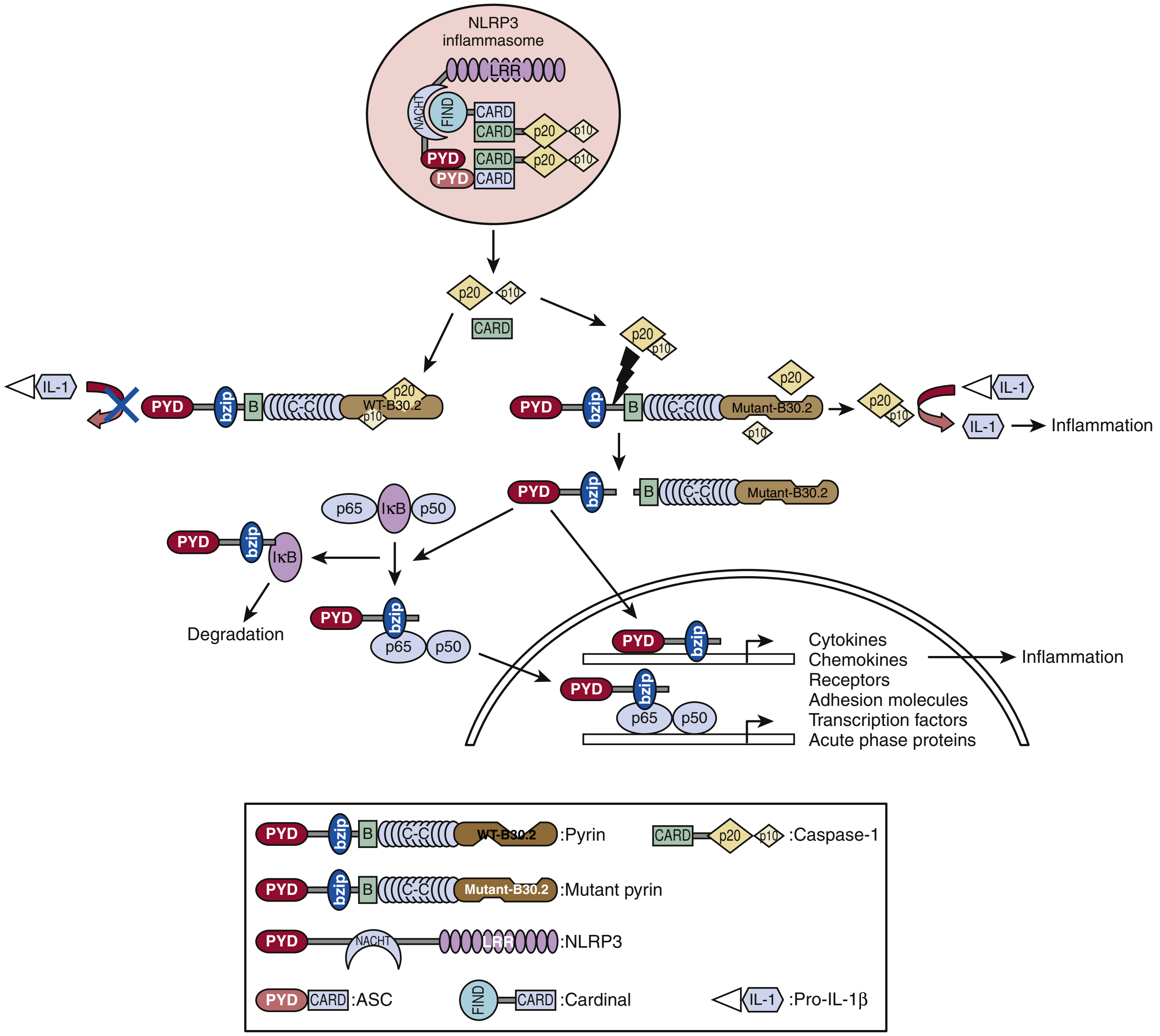


**FIGURE 80-4** Proposed role of pyrin in the pathogenesis of familial Mediterranean fever (FMF). The structural organization of a representative inflammasome (NLRP3) is shown. The active caspase-1 subunits p10 and p20 are produced in the inflammasome by inducing proximity-mediated autocatalysis. The wild-type B30.2 domain of pyrin interacts with the p20 and p10 subunits and, as a consequence, prevents formation of an active p20/p10 heterodimer. FMF-associated pyrin B30.2 mutants interact with p20 and p10 but to a lesser extent than does the wild-type B30.2 domain, therefore enabling p20/p10 heterodimer assembly, IL-1β activation, and induction of inflammation. The active p20/p10 heterodimer cleaves pyrin at Asp330 (located between the bZIP basic domain and the B-box zinc finger domain). The N-terminal–cleaved fragment interacts with p65 and IκB kinase α (IκBα) through the bZIP basic domain and adjacent sequences, by which NF-κB is activated with induction of inflammatory genes expression. IL-1β, interleukin-1β; NF-κB, nuclear factor κ light-chain enhancer of activated B cells. (Adapted with permission from Chae JJ, Aksentijevich I, Kramer DL: Advances in understanding of familial Mediterranean fever and possibilities for targeted therapy, *Br J Haematol* 146:467-478, 2009.)

amyloid A (SAA) protein, whose production is markedly increased in chronic inflammatory processes.[150] Amyloidosis is frequently found in Jews from North African countries in the ME, in Turks, and in Armenians. As mentioned earlier, a positive association of amyloidosis with the *M694V* mutation has been reported in patients from several ethnic gro ups.[122,124,129,131,135,136,151] The *M694V* mutation has also been detected in patients with FMF phenotype II: the manifestation of amyloidosis before the onset of clinical symptoms of FMF.[136] A screening of patients with FMF from 14 countries worldwide—which included Israel, Turkey, Qatar, Jordan, and Lebanon—revealed that amyloid nephropathy was present in 11.4% of patients with FMF.[152] In this study, however, the country of recruitment, rather than *MEFV* genotype, was found to be the leading risk factor for amyloidosis.[152]

Male gender, a positive family history of amyloidosis, pain flares in joints, and the SAA1 α/α genotype have been suggested as additional risk factors for amyloidosis.[153] Albuminuria is usually the first manifestation of renal involvement in patients with FMF and amyloidosis, and in untreated patients, it may appear early in the course of FMF.[154] The proteinuria is represented mostly by albumin, and values can

reach the nephrotic range, with urinary protein excretion rates higher than 20 g/day. If untreated, AA amyloidosis progresses to ESRD that ultimately may necessitate RRT. Extrarenal deposits of AA amyloid can be found in liver, spleen, lung, thyroid, heart, adrenal glands, stomach, and testes. These deposits can be clinically significant and are associated with intestinal malabsorption and adrenal insufficiency that are often diagnosed after the initiation of chronic hemodialysis or after kidney transplantation.[154-156]

The diagnosis of amyloidosis can be confirmed by tissue biopsy; the sensitivities of the rectal or bone marrow biopsy and renal biopsy are 79.5% and 88%, respectively, whereas the sensitivity of biopsy of abdominal fat is lower.[157-159] The presence of amyloid deposits is demonstrated histologically with Congo red staining of the biopsy tissue sample. Congo red—stained amyloid has an orange appearance when viewed under a light microscope and an apple-green birefringence when viewed under polarized light. Another amyloid-specific stain, thioflavin T, is used less frequently than Congo red. Amyloidosis is diagnosed definitively on electron microscopy by the demonstration of characteristic amyloid fibrils. The AA protein in tissue can also be detected with antibodies against AA protein.[158]

In addition to AA amyloidosis, other kidney diseases have been diagnosed in patients with FMF. It is worthwhile mentioning that many of the reports of systemic and inflammatory diseases in patients with FMF contain descriptions of kidney involvement.[136] In fact, the frequency of the reported nonamyloid glomerular lesions reflects the number of kidney biopsies that are performed in patients with abnormal findings on urinalysis or on kidney function tests. Recurrent focal and proliferative glomerulonephritis and polyarteritis nodosa were described in an early report of the disease.[160] Rapidly progressive glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, and membranous nephropathy have also been reported.[136,140,161-164]

### Treatment of Familial Mediterranean Fever

Daily oral colchicine is the most effective therapy for patients with FMF, and its use since the 1980s has dramatically changed the course of the disease. Colchicine prevents both acute attacks of FMF and SAA amyloidosis.[165,166] The mechanism of colchicine action is not well understood. It is believed that one of its major actions is to interact with cytoskeletal structures, such as microtubules. It has been shown that colchicine accumulates in PMNCs, where it depolymerizes the microtubules and suppresses microtubule dynamics. Pyrin is also expressed in PMNCs and associates with microtubules.[167] Because colchicine also has an inhibitory effect on chemotaxis and reduces serum levels of IL-6, IL-8, and tumor necrosis factor-α,[168] its antiinflammatory action is thought to be related to its ability to suppress NF-κB activation by the attenuating calpain-mediated IκB kinase α degradation, which is enhanced by N-terminal cleaved pyrin.[144]

The most common adverse effects of colchicine are gastrointestinal, especially abdominal pain and diarrhea. Colchicine toxicity from overdosing is associated with hepatic, renal, muscle, and cerebral effects.[169] Nonresponsiveness to colchicine has been reported in 5% to 10% of patients. The reasons for nonresponsiveness are complex and include noncompliance, socioeconomic factors, and clinical factors. The results of one study revealed the existence of an association between polymorphism of adenosine triphosphate–binding cassette, subfamily B, member 1 *(ABCB1)* gene and the response to colchicine in Turkish patients with FMF. The *ABCB1* gene encodes p170 (also known as multidrug resistance 1 [MDR1]), a glycoprotein that functions as a drug transport pump, which can cause a variety of drugs, including colchicine, to become extruded from cells. In this study, patients with FMF who had the TT genotype for the 3435C→T variant of *ABCB1* responded better to colchicine in terms of treatment efficacy and lower dose requirements in comparison with patients who had the CT and CC genotypes.[170] These results warrant validation in further studies in patients with FMF from different ethnic populations.

Thalidomide, azathioprine, and eprodisate disodium, an inhibitor of fibril formation, are occasionally used to treat patients with FMF whose disease is refractory to colchicine.[171-173] Interferon-α was one of the first drugs that was used to treat patients with FMF who were refractory to colchicine.[174] Two studies of patients with FMF who were treated with interferon-α showed that the duration and pain intensity of the majority of the attacks were reduced by more than 50%.[175,176] In addition, clinical improvement has been reported in patients with FMF who were treated with the tumor necrosis factor-α antagonists etanercept or infliximab.[171,177,178] Because most inflammatory manifestations of FMF are believed to be associated with the induction of IL-1β production by mutations in the C-terminal B30.2 domain of pyrin (see Figure 80-4), it has been proposed that IL-1β antagonists may be an effective therapy for FMF. The IL-1β receptor antagonist anakinra has been shown to have a beneficial effect in patients with cryopyrin-associated periodic syndromes.[179] Indeed, significant improvement and resolution of FMF symptoms have been reported in patients with colchicine-resistant FMF who were treated with anakinra.[180,181] In one of these cases, anakinra elicited a beneficial therapeutic response in a patient with FMF who was undergoing maintenance hemodialysis and after kidney transplantation.[181] The main limitation of anakinra treatment in patients with FMF is probably the need for daily subcutaneous injections. Administration of either the long-acting IL-1 antagonist rilonacept (IL-1 Trap) every week or the administration of canakinumab, a human monoclonal antibody against IL-1β every 8 weeks has also been associated with rapid remission of symptoms in cryopyrin-associated periodic syndromes.[182,183] Therefore, these therapeutic antibodies could have beneficial effects in patients with refractory FMF.

### Familial Mediterranean Fever and End-Stage Renal Disease

In contrast to the poor prognosis of patients with primary (AL) amyloidosis who require RRT, most patients with FMF and secondary (AA) amyloidosis do relatively well with chronic dialysis.[184] However, the issue of which dialysis modality is the ideal for the treatment of FMF-associated ESRD is still unresolved,[40] and prospective studies that compare the different dialysis modalities are still needed. Of the dialysis modalities, hemodialysis is more widely used in patients with FMF. Continuous ambulatory peritoneal dialysis (CAPD), however, has been performed successfully in selected patients. The effects of CAPD on azotemia and overall survival are similar in patients with nonamyloid diseases and patients with FMF. However, the serum albumin levels are reported to be lower, and the rate of peritonitis and requirements for erythropoietin-stimulating agents (ESAs) were higher in patients with

FMF who received CAPD than in patients with FMF who received hemodialysis.[185,186]

A considerable number of patients with FMF and ESRD have undergone kidney transplantation in the last few decades. The rates of survival of patients and allografts FMF are reported to be worse or similar to those in the general population of kidney transplant recipients.[40,136,187-190] Maintenance colchicine therapy is obligatory after kidney transplantation because it may prevent the recurrence both of FMF symptoms and of amyloidosis. However, recurrence of AA amyloidosis has been frequently reported 8 to 10 years after kidney transplantation,[191] and the rate of recurrence may be as high as 71%.[190] Adverse drug effects are seen in kidney transplant recipients with FMF who are taking cyclosporine. In addition, increased gastrointestinal complications can be observed in patients who are treated with a combination of mycophenolate mofetil and colchicine.[192]

## Management of End-Stage Renal Disease in the Middle East

Dialysis and kidney transplantation are available in all ME countries. In all industrialized and many developing ME countries, RRT is accessible to every patient with ESRD, regardless of the patient's socioeconomic status or whether the patient has health insurance.[8,21,49,50,52,55,57,59,193-195] On the other hand, the number of patients offered RRT in other developing ME countries may be affected by late diagnosis and referral, the presence of comorbid conditions, the country's health system, reimbursement, and the availability of dialysis facilities.[59]

### Dialysis

#### Peritoneal Dialysis

Throughout the ME, hemodialysis is the preferred treatment modality for established ESRD (see Table 80-4). Peritoneal dialysis is an underused treatment modality for ESRD, although its use is increasing in Tunisia, Kuwait, Iran, Saudi Arabia, and Turkey.[194,196,197] Several medical and nonmedical factors play an important role in inhibiting the widespread use of peritoneal dialysis throughout the ME: (1) Health providers generally offer low or no reimbursement for peritoneal dialysis; (2) the numbers of peritoneal dialysis training programs, qualified nephrologists, and skilled dialysis nurses are limited, and the salaries of attending physicians for peritoneal dialysis are low; (3) many patients have poor education and poor hygiene practices; and (4) patients and caregivers have concerns about high rates of peritonitis.

At the end of 2006, 38,824 patients were treated with dialysis (87.4% with hemodialysis, 12.6% with peritoneal dialysis) in Turkey, and 99.7% of all patients receiving dialysis are covered by the social security system.[193] The Turkish experience in establishing a peritoneal dialysis program has been outstanding and could be used as an example by other ME countries. The Turkish Multicenter PD Study Group (TULIP) has established a platform for organizing peritoneal dialysis facilities and units. The group helped standardize patient records and various peritoneal dialysis treatments and maximized the number of patients with ESRD who can benefit from this treatment modality. This group has published clinical research that has affected peritoneal dialysis practice locally and worldwide.[193] The Turkish peritoneal dialysis program has good rates of survival of patients and technique efficacy, which are comparable with those in Western industrialized countries.[198] The peritoneal dialysis dropout rate was 21%, and the incidence of peritonitis was one episode per 35.5 patient months in 2007. Dyslipidemia was the most common noninfectious complication[48]; cardiovascular diseases (42.3%), followed by infections (19.9%) and cerebrovascular events (13.6%), were the major causes of death among Turkish patients undergoing peritoneal dialysis.[48,198] Moreover, peritoneal dialysis has been suggested as a means of reducing the seroconversion rate for hepatitis C virus (HCV) in populations with ESRD and a high prevalence of infection[199]; such treatment thereby confers an advantage to kidney transplant candidates.[200]

Peritoneal dialysis was started in Iran in 1978 and in Saudi Arabia and Kuwait during the 1980s with imported peritoneal dialysis solutions. The costs of this treatment are low in Turkey and Iran because peritoneal dialysis solutions began to be produced locally in Turkey in 1994 and in Iran in 1995.[196] Establishment of a peritoneal dialysis registry and a multidisciplinary approach has dramatically increased the numbers of patients undergoing peritoneal dialysis in Iran since 2001. The peritonitis rate in these patients is reported to be one episode per 19.4 patient months, and the dropout rate is 11%; dropout is caused mainly by infectious complications.[196] The 1-year, 3-year, and 5-year patient survival rates in Iran were reported as 88%, 68%, and 49%, respectively, whereas technique survival rates were 79%, 41%, and 24%.[196]

#### Hemodialysis

There are limited published data on hemodialysis in the ME with regard to the practice patterns and outcomes, such as the quality of dialysis, the survival of patients per technique, the type of vascular access, the standard dialysate solutions and dialyzers, medical complications and their management, comorbid conditions, and other parameters of quality assurance.[57] In general, quality is ensured according to best medical practice guidelines that exist in industrialized ME countries with more resources, easily accessible health care systems, and advanced medical supplies, such as those found in Israel. In ME countries that lack resources, prescription of hemodialysis is minimal and the quality of dialysis is dictated by nonmedical financial considerations. In these countries, dialysis may be offered only once or twice weekly, and the underlying reasons can be, among others, the lack of skilled personnel, the distance of the dialysis centers from the patient's residence, and whether the patient pays for the treatment. On this last point, the number of patients who withdraw from hemodialysis therapy because of financial problems has not been documented. Nonetheless, a small number of patients do seek pre-ESRD care in most ME countries.[3,57]

According to the 2010 SCOT report,[53a] 11,437 patients receiving hemodialysis were treated in 177 centers in which 4481 hemodialysis machines are available in Saudi Arabia. Of these patients, about 22% are on the waiting list for kidney transplantation. Bicarbonate dialysis solutions are used in all centers, and only a few centers (6.3%) still use acetate dialysis solutions. The predominant type of vascular access for hemodialysis is arteriovenous fistulas (71.2% of all patients), followed by jugular catheters (12.6%) and arteriovenous

grafts (7.6%). In comparison, the prevalent types of vascular access in Israel in 2007 were arteriovenous fistulas (57.6%), arteriovenous grafts (16.3%), and permanent and temporary catheters (24.4% and 1.6%, respectively).[200a] In Tehran, arteriovenous fistula is the type of vascular access used most in patients receiving hemodialysis (91%); only 3% of such patients have arteriovenous grafts, and 4% have permanent catheters.[52] Arteriovenous fistula is also preferred in Turkey: in 2007, arteriovenous fistula were used in 85.7% of Turkish patients receiving hemodialysis, grafts were used in 2.9%, permanent tunneled catheters were used in 6.9%, and temporary catheters were used in 4.2%.[200b]

Reuse of dialyzers is not practiced in Saudi Arabia and Iran[201] and is prohibited by law in Egypt.[57]Approximately 87% of Saudi patients receiving hemodialysis are treated with ESAs, and of these patients, about 23% of the patients have hemoglobin levels lower than 10 g/dL. In comparison, 48.2% of patients receiving hemodialysis in Tehran have anemia as a result of low-dose treatment with ESAs, and dialysis may be inadequate because the mean measurement of treatment adequacy (Kt/V) for these patients was 0.97 ± 0.25.[52] Barsoum[59] estimated that 0% to 10% of patients undergoing hemodialysis receive erythropoietin in North African countries in the ME. In Turkey, ESAs are administered to 61.8% of patients receiving hemodialysis. The results of a comprehensive study of 2630 patients receiving dialysis (mainly hemodialysis) from Tehran province provide some insight into the treatment of ESRD in Iran[52]: The common clinical practices for hemodialysis are almost concordant with the international guidelines but do not reach all the recommended targets.

No studies have been well conducted to describe the patterns, prevalence, or therapy of mineral and bone disorders in patients undergoing dialysis in any of the 20 ME countries. In developing ME countries, the aluminum-based phosphate binders presence of high amounts of strontium in the soil and the use of dialysis acetate concentrates that are contaminated with strontium have been implicated as a cause of osteomalacia in adult patients receiving hemodialysis and a cause of rickets in pediatric patients receiving hemodialysis.[202,203] Hyperphosphatemia and increased serum calcium-phosphorus product are serious problems in dialysis recipients in developing ME countries, and their occurrence is correlated with poor patient knowledge of appropriate diet. In a large cross-sectional multicenter study that included 1005 patients in Egypt who were undergoing hemodialysis, two thirds of the patients had hyperphosphatemia, and one third had an elevated serum level of calcium-phosphorus product. The patients used mainly calcium-based phosphate binders.[204] In most developing ME countries, economic considerations hinder the use of the newer non–calcium-based phosphate binders, calcium-sensing receptor agonists (calcimimetics), or vitamin D receptor agonists. Therefore, prolonged or additional dialysis sessions are frequently prescribed to control hyperphosphatemia in patients receiving hemodialysis.[52,204]

The results of one survey suggested that practicing Saudi nephrologists have an adequate perception of the morbidity in patients with CKD and mineral and bone disorders.[205] However, the results of this survey proved the need for creating national guidelines because the physicians' assessment of the prevalence, patterns and results of therapeutic interventions in patients with CKD and mineral and bone disorders was relatively inadequate. About 25% of their patients had hyperphosphatemia (serum phosphorus levels >6 mg/dL), and 20% had hypocalcemia (serum calcium levels <8.4 mg/dL), although vitamin D was administered orally to most patients.

## Management of End-Stage Renal Disease with Viral Hepatitis

Available global data indicate that the prevalence of chronic infection with hepatitis B virus (HBV) and HCV is high in populations of the African and ME regions (Table 80-8).[206,207] These two viral infections have considerable effects on morbidity and mortality among patients with ESRD, as well as on graft survival in kidney transplant recipients.[57,208-211] However, surveys are still needed to correctly estimate the incidence and prevalence of these infections in patients with CKD and ESRD in each ME country. In addition, screening will identify patients who will benefit from treatment. The HCV epidemic is particularly devastating in Egypt, where its prevalence in the general population is estimated to be more than 18% (see Table 80-8) and as high as 60% among dialysis and kidney transplant recipients.[57,212] The start of the HCV epidemic in Egypt is attributed to the use of unsterilized needles and syringes during the mass antischistosomiasis treatment programs that were conducted during the 1960s and 1970s.[213]

Among Saudi patients receiving hemodialysis, according to the 2010 SCOT report,[53a] the prevalence of HBV positivity is relatively low (4.1%), whereas HCV infection continues to be problematic (24.5 %). However, there is a considerable

**TABLE 80-8 Prevalence of Hepatitis C Infection in Middle East Populations**

| COUNTRY | INFECTION RATES (%) |
|---|---|
| Algeria | 0.2 |
| Bahrain | NA |
| Egypt | 18.1 |
| Iran | NA |
| Iraq | 0.5 |
| Israel | 0.4 |
| Jordan | 2.1 |
| Kuwait | 3.3 |
| Lebanon | NA |
| Libya | 7.9 |
| Morocco | 1.1 |
| Oman | 0.9 |
| Palestinian Authority | 2.2 |
| Qatar | 2.8 |
| Saudi Arabia | 1.8 |
| Syria | NA |
| Tunisia | 0.7 |
| Turkey | 1.5 |
| United Arab Emirates | 0.8 |
| Yemen | 2.6 |

*NA,* Not available.

Data from Hepatitis C—global prevalence (update), *Wkly Epidemiol Rec* 74(49): 425-427, 1999.

variability in the prevalence of HCV infection between the various hemodialysis centers (15% to 80%).[208,214] This variability is important to consider when patients receiving hemodialysis travel to other units and emphasizes the importance of screening them for seroconversion after their return. The annual rate of HCV seroconversion in Saudi patients receiving hemodialysis is between 7% and 9%. The most common variant of the virus is HCV genotype 4 (which is also prevalent in North African countries in the ME[57,209]), followed by HCV genotype 1a and HCV genotype 1b. Implementation of strict measures of infection control and isolation of HCV-positive patients and dialysis machines resulted in a significant drop of the annual incidence of HCV infections from 2.4% to 0.2% in one Saudi hemodialysis center.[214]

In Iran, where genotypes 3a and 1a are the common variants, impressive drops in the rates of HCV and hepatitis B surface antigen (HBsAg) positivity have been reported in patients receiving hemodialysis. These drops (14.4% in 1999 to 4.5% in 2006 for HCV and 3.8% in 1999 to 2.6% in 2006 for HBV) have been attributed to the introduction of several measures, such as strict isolation policies, no reuse of dialyzers, compulsory HBV vaccination in patients, and early kidney transplantation.[201] Implementation of routine virology testing, strict isolation measures, HBV vaccination, and ESA administration with few blood product transfusion requirements have resulted in a low prevalence of both HBV (1.9%) and HCV (4%) infection among Israeli patients receiving dialysis in 2007, according to the 2009 ICDC report.[200a]

Using second-generation immunoassays to detect HCV infection in 30 Turkish dialysis centers, Köhler[208] found that the prevalence of HCV was 49.9% in 1995. Sayiner and colleagues[215] reported that the duration of dialysis, kidney transplantation history, and history of blood products transfusion were all related to HCV transmission and high prevalence of HCV among Turkish patients receiving hemodialysis. Turkey is also endemic for HBV infection. Ten percent of patients receiving hemodialysis and 2.9% of blood donors are HBsAg positive. Of note is that the 2007 registry of the Turkish Society of Nephrology[200b] reported a decline in the prevalence of HBV infection (4.9%), HCV infection (13.2%), and both infections (1.6%) in Turkish patients receiving hemodialysis. The results of a survey that was conducted among Jordanian patients receiving hemodialysis during 2003 revealed HBV positivity in 4% and HCV positivity in 21%, with annual seroconversion rates of 0.34% for HBV and 2.6% for HCV.[55]

In comparison, the adjusted prevalence of HBV is 4.6% among patients in Germany who are undergoing hemodialysis, 4.3% in Italy, 3.7% in France, 2.1 % in Spain, 2.1% in Japan, and 2.4% in the United States, and adjusted seroconversion rates range from 0.4 to 1.8 per 100 patient-years.[216] The adjusted prevalence of HCV also varies among these countries: 22.9% in Spain, 20.5% in Italy, 10.4% in France, 3.8% in Germany, 2.6% in the United Kingdom, 14.8% in Japan, and 14% in the United States.[217] The adjusted seroconversion rates range from 1.2 to 3.9 per 100 patient-years and are highest in Italy and Spain.[217]

### Dialysis-Related Outcomes

With regard to other dialysis-related outcomes, reports from Egypt have revealed significant center-specific effects (which were not defined) on the survival and quality of life of patients receiving dialysis; these effects were dependent largely on funding.[57] In Syria, the 3-year survival rate among patients receiving hemodialysis was unsatisfactory, ranging from 26% to 64% in different hemodialysis centers.[194] In Jordan, the 1-year mortality rate among patients receiving hemodialysis is approximately 20%.[55] According to the 2009 ICDC report,[200a] the unadjusted 1-year, 2-year, 3-year, and 10-year survival rates among Israeli patients receiving dialysis were 80%, 66.6%, 54.9%, and 10%, respectively, from 1990 to 2007.

Of interest is that a health disparity exists for both legal and illegal immigrants from ME countries with CKD who live and work in Western industrialized countries and may need RRT. The ethnic and educational backgrounds of these patients are different from those of the local population. Accordingly, they face potential problems with communication, health insurance, and care.[5] Fogazzi and Castelnovo[218] reported their experience with such patients who were treated in an Italian dialysis unit. Although the number of patients was small, they reported that those receiving hemodialysis who came from developing countries, which included some ME countries, were younger at the initiation of dialysis (38.2 ± 7.9 years vs. 63 ± 12.6 years), were referred at a later stage of their disease, and had more infections, such as tuberculosis and viral hepatitis, than did patients from the local population who were undergoing hemodialysis. Furthermore, they also reported that a visit to their native countries was usually associated with medical complications, such as worsening of anemia.

## Kidney Transplantation

In ME countries, as in all other countries, kidney transplantation is recognized as the treatment of choice for ESRD. The beneficial effects of kidney transplantation on life expectancy, quality of life, and medical expenses are greater than those associated with maintenance dialysis. However, legislative obstacles, an underdeveloped and poorly funded health infrastructure, poor public awareness of the importance of organ donation, lack of effective kidney transplantation programs, cultural and religious barriers, and lack of trained multidisciplinary medical teams are some of the obstacles that prevent the promotion of kidney transplantation in some ME countries.[219,220]

Most ME countries are members of the Middle East Society for Organ Transplantation (MESOT). MESOT includes Iran, Turkey, and all of the Arab countries in the ME, as well as Pakistan, Cyprus, and some countries of central Asia.[219] There are very few organ procurement centers in the MESOT member countries for overseeing the activities of organ donation, sharing, and transplantation at a national level. Israel is not a member of MESOT; it has its own National Center for Organ Transplantation. The first successful cadaveric kidney transplants in the ME were performed in 1966 in Haifa, Israel,[221] and were reported to have been performed in 1967 in Shiraz, Iran.[222] The first successful kidney transplantation in an Arab country in the ME was performed with a kidney from a deceased donor with no heartbeat in Jordan in 1972. Most other ME countries, such as Lebanon and Turkey, started their kidney transplantation programs during the early 1970s, and Egypt and Saudi Arabia commenced their programs in 1976 and 1979, respectively. Since then, the remaining ME countries have established their own kidney transplantation programs; Libya was the country to do so most recently, in

2004. Currently, kidney transplantation programs and practices are active in most ME countries but are relatively limited in Algeria, Yemen, the UAE, and Bahrain.[197,223-225]

Most kidneys for transplantation are harvested from living donors. An important milestone that paved the way for organ donation for transplantation from deceased donors in the Arab countries in the ME was the Amman Declaration in 1986. In this declaration, Islamic theologians recognized that brain death was irreversible and could be used to declare a person legally dead, thereby making it permissible to disconnect that person from mechanical life-support systems. This declaration was preceded in 1982 by a resolution of the Islamic Council in Saudi Arabia that permitted the harvesting and transplantation of organs from both living and deceased donors.[197,226] Similar declarations have since been made by religious authorities in Egypt, Turkey, and Iran.[197,226] As a result of these declarations, most Arab countries in the ME, except Egypt, have now enacted laws for regulated organ donation for transplantation from both living and cadaveric donors, and transplantation programs for kidneys and other organs are beginning to expand.

In his code of Jewish law, the Mishneh Torah (Laws of Sanhedrin, 12:3), the twelfth century philosopher and physician Maimonides interpreted the Talmud as saying that someone who saves the life of one person is considered to have saved the entire world. This is similar to what is written in the Koran, Chapter 5, verse 32: "…if any one saved a life, it would be as if he saved the life of all mankind." Therefore, organ donation that saves life is considered in Islam and Judaism to be a good deed. With regard to living-related donors, Bulka[227] argued that organ donation is permissible, because the danger to the donor is minimal, but it is not obligatory. Likewise, Christians believe that organ donation is an act of love and nobility (e.g., as interpreted from Corinthians and from the parable of the Good Samaritan in Luke, Chapter 10, verses 25 to 37).[228]

Active deceased-donor kidney transplantation programs exist in Iran, Jordan, Kuwait, Lebanon, Saudi Arabia, Tunisia, Turkey, and Israel. However, deceased-donor kidney transplantation is inadequate to address the current need for allografts, and the number of patients on kidney transplantation waiting lists in these ME countries is progressively increasing. The use of kidneys from living-related donors is increasing, but the gap between demand and supply is continuously widening in all ME countries. In order to meet the growing demand for kidneys and the shortfall in donors, some countries have initiated kidney transplantation programs involving organs from living-unrelated donors. Using emotionally related donors extends donor eligibility to include individuals who are not genetically related to recipients.

Although kidney transplantation involving organs from deceased donors is increasing in the ME, it accounts for less than 30% of kidney transplantations in most ME countries, with large national variations. In 2007, of the kidneys that were harvested for the 1316 kidney transplantations that were performed in Turkey, 33.2% were from deceased donors, according to Turkey's national registry. In Saudi Arabia, kidney transplantation from living-unrelated donors is forbidden. SCOT reported that 505 kidney transplantations were performed in 2010, and 31% of the kidneys were harvested from deceased donors[53a]; the rest were obtained from living-related donors. In fact, in 2006, Saudi Arabia had the highest reported rate of living-donor kidney transplantation worldwide at 32 procedures per million population, followed by Jordan (29 procedures per million population), Iceland (26 procedures per million population), Iran (23 procedures per million population), and the United States (21 procedures per million population).[195] However, the quoted Saudi statistic should be interpreted cautiously because the rate of living-related donor kidney transplantations is 10.1 per million population. According to Nöel,[229] Horvat and colleagues[195] probably included "transplant tourism" activity because they incorporated data on kidney transplantations in Saudi patients from living-unrelated donors that were performed in other countries into their rates of kidney transplantation in Saudi patients.

In Egypt, about 7% of Egyptian patients with ESRD are offered kidney transplantation in the year of diagnosis, and no kidneys are harvested from deceased donors: 80% of the kidneys are obtained from living-unrelated donors, and 20% are obtained from living-related donors. In 2007, 127 kidney transplants were performed in Israel; of the transplanted kidneys, 46.5% were obtained from deceased donors and 53.5% from living-related and living-unrelated donors.[230] However, the ratio of deceased donors to living donors is not constant. In fact, this ratio was reversed in 2008, according to the annual report of the Israeli National Transplant Center: 156 kidney transplantations were performed; 65% of the kidneys were obtained from deceased donors and 35% from living donors.

Kidney transplantation in Syria commenced in 1976 with exclusive reliance on kidneys from living-related donors. Since 2003, transplantation of kidneys from deceased donors has been allowed. As of 2005, 13 per million population kidney transplants were performed, a rate lower than that in Western industrialized countries (20 to 40 per million population).[194,197]

In Iran, the living-unrelated donor transplantation program operates under the close supervision and scrutiny of the Ministry of Health and Medical Education, the Iranian Scientific Society of Organ Transplantation, the Foundation for Patients with Special Diseases, and Dialysis and Transplant Patients Association (DATPA).[231] In the "Iranian model," patients who need kidney transplantation are referred to the DATPA, a charity founded in 1978 by Iranian patients with ESRD, which acts as a liaison agency between patients and potential donors. The altruistic volunteers are also registered by the DATPA and undergo evaluation in the foundation's clinics. Several important features characterize the "Iranian model" of living-unrelated donors for kidney transplantation: No coercion is allowed; written consent is obtained from the donor and the donor's parents or spouse; donors are rewarded with gifts from the government; no commercialism is allowed; the medical teams receive no financial benefit; recipients and donors must be Iranian citizens; and time on the waiting list is minimal.[223,232] Consequently, the annual number of kidney transplantations has substantially increased in Iran. In parallel, the number of deceased-donor kidney transplants increased from 1% in 2000 to almost 13% in 2006, and the kidney transplantation rate reached 26.5 per million population in 2006.[223] Ten years after the introduction of the controlled living-unrelated donors kidney transplantation program in Iran, the national waiting list for renal transplants was eliminated.[196,233]

Simforoosh and associates[234] reported that patient and graft survival of 2155 Iranian recipients of kidneys from living-unrelated donors after 15 years were 76.4%, and 53.2%,

respectively. These results are comparable with survival data in the 2003 annual report of the United States Renal Data System on living-donor kidney transplants.[235] However, the “Iranian model” has been criticized for ethical reasons because 85% of the vendors are very poor, a fact that may increase the risk that potential donors will withhold relevant medical information.[236] In addition, altruistic kidney donation has decreased because the psychologic consequences of organ vending in Iran have been found to have negative effects on the donor.[237]

## Commercial Kidney Transplantation

The lack of deceased donors for kidney allograft transplantation, combined with other medical factors (prolonged graft survival and improved surgical techniques, including laparoscopic nephrectomy) and nonmedical factors (economic and cultural), have motivated a large number of patients with ESRD to seek kidney transplants from living-unrelated donors outside their home countries. This practice is often called “commercial kidney transplantation” or “organ tourism” because the donor sells his or her kidney for a certain amount of money. These kidney transplants are performed in many countries around the world, such as the Philippines, Russia, India, China, Pakistan, and South Africa, as well as some ME countries, such as Turkey, Iraq, and Egypt.[197,238-240] The surgery is commonly performed in substandard conditions under the cover of secrecy. Many transplant recipients return to their homelands 1 to 2 weeks after transplantation without crucial information (a complete medical report; important information about the donor; HLA typing; and details of the medical treatment, surgery, and postoperative care). In addition, the recipients are exposed to potential risk of infection, such as HBV, HCV, or human immunodeficiency virus (HIV) infection, as well as tuberculosis from inadequately evaluated vendors. Thus the results of such commercial kidney transplantations are reported to be substandard.[238-240]

In order to undermine the practice of global commercial kidney transplantation, the Transplantation Society and the International Society of Nephrology convened an international summit meeting in Istanbul, Turkey, in April 2008. The outcome of this meeting was the “Declaration of Istanbul on Organ Trafficking and Transplant Tourism,” which suggested that strategies to increase the donor pool and encourage legitimate, lifesaving transplantation programs be developed by countries in order to prevent organ trafficking, transplant commercialism, and transplant tourism. In addition, these strategies should be aimed at stopping and prohibiting these unethical activities, as well as encouraging safe and accountable practices that both meet the needs of transplant recipients and protect donors.[241,242] Many ME countries need to develop national self-sufficiency in organ donation in order to combat organ tourism and achieve global justice in transplantation.[242]

## Pharmacologic Treatment of Kidney Transplant Recipients

In general, all approved medications that are used worldwide to treat kidney transplant recipients are also used in the ME.[225] In all ME countries with kidney transplantation programs, induction therapy with methylprednisolone, lymphocyte-depleting agents, or interleukin-2 receptor antagonists is widely used. In most of the commercial transplantation programs, induction therapy is routinely given in order to reduce the frequency of acute graft rejection so that the recipient can be discharged early after the transplantation surgery. No reports have yet been published on the long-term complications of this routine treatment, such as bone marrow suppression, cytomegalovirus infections, and posttransplantation lymphoproliferative disorder.

Maintenance treatment after kidney transplantation in ME countries consists of triple therapy with corticosteroids, azathioprine or mycophenolate mofetil, and calcineurin inhibitors. For economic reasons, several countries prefer to prescribe azathioprine and the cheap generic forms of cyclosporine instead of mycophenolate mofetil and tacrolimus. A small number of kidney transplantation centers have started prescribing rapamycin, a drug that inhibits a serine/threonine kinase called the mammalian target of rapamycin (mTOR), to prevent transplant rejection.[226] Treatment of acute rejection in most ME countries consists mainly of methylprednisolone (Solu-Medrol) and rabbit antithymocyte globulin (Thymoglobulin). Hyperimmune globulins and plasmapheresis are rarely used because both are expensive.

## Posttransplantation Complications

There are only a few reports in the literature on the outcomes, as well as patient and graft survival rates, after kidney transplantation in ME countries. In general, these reports claim that outcomes in Saudi Arabia, Kuwait, Egypt and North African countries in the ME are in line with international standards, although infections remain the main reason for morbidity and mortality among these patients.[8,59,234,240,243] Distinctive infections are of special concern in some ME countries. Tuberculosis is prevalent among dialysis recipients in some countries such as Saudi Arabia, Yemen, Turkey, and the North African countries in the ME.[220,244-248] Patients in these countries are at increased risk for developing active tuberculosis after kidney transplantation, and about 30% have symptoms of tuberculosis in extrapulmonary organs, particularly the lymph nodes, gastrointestinal tract, and peritoneal cavity. The Mantoux test often yields negative results in kidney transplant recipients, possibly because of the suppression of cellular immunity. Tuberculosis in the graft kidney tends to manifest as granulomatous interstitial nephritis. Urinalysis results are often negative for bacilli. The diagnosis is usually made on kidney biopsy or after nephrectomy in recipients, who often present with fever of unknown origin and deteriorating graft function.

Prophylactic treatment with isoniazid or rifampin for patients at high risk (Mantoux skin test reaction of >10 mm) has decreased the development of active tuberculosis. An important sequela of this treatment is the induction of cytochrome P450 enzymes by the antituberculous drugs, which results in a severe drop in the circulating therapeutic levels of calcineurin inhibitors and, consequently, severe acute rejection. Therefore, increasing the dose of calcineurin inhibitors and frequent monitoring of their circulating levels are mandatory in such cases.[220,244,245]

Viral hepatitis, as discussed previously, is also common in the ME, especially among patients receiving dialysis. Eligible patients with HBV and HCV infections are offered

transplantation in many ME kidney transplantation centers after appropriate presurgical workup and management.[212,245]

The most common types of neoplasia among kidney transplant recipients are skin malignancies, lymphoproliferative disorders, and Kaposi's sarcoma. The incidence of some uncommon tumors in the general population (e.g., Kaposi's sarcoma) can be 400- to 500-fold higher among kidney transplant recipients. Kaposi's sarcoma is most often seen in transplant recipients of Mediterranean, Jewish, and Arabic descent. Its reported incidence is 0.5% in most Western industrialized countries and as high as 5.3% in Saudi Arabia.[245,249-251] The preponderance of cases of Kaposi's sarcoma in certain ethnic groups appears to be linked to the geographic distribution of human herpesvirus 8 infection, inasmuch as more than 80% of transplant recipients with Kaposi's sarcoma are seropositive for human herpesvirus 8 before undergoing transplantation.[249]

## Summary

The ME has a strategic global location. Its fascinating geography is combined with rich national histories, cultures, and resources. In addition, the countries of ME differ in their economics, political systems, culture, and bioecology, all of which eventually translate into disparities in their health systems, as well as in disease epidemiologic features, causes, management, and outcomes. The burden of kidney diseases is high in all ME countries and is compounded by many risk factors in the region, although data from developing countries are possibly underestimates. Practicing nephrologists in the ME are familiar with the genetic background, social habits, and culture of their patients. However, this is not so for many individuals of ME origin who now live in non-ME countries. Nephrologists in those countries need to take these considerations into account when diagnosing or treating the kidney diseases and comorbid conditions of their patients of ME origin. Therefore, the emerging epidemic of diabetes mellitus in many ME countries is pertinent, and the prevailing genetic kidney diseases in the various population groups who live in the ME have been reviewed in this chapter.

Moreover, the ME has experience in management of mass disasters and consequent kidney complications, which can be implemented in regions outside of the ME. However, several issues still need to be addressed and hurdles must be overcome in order to improve the overall management of kidney diseases in the ME. Well-conducted epidemiologic cohort studies are urgently needed, and regional and national registries must be established as sources of transparent and accurate data. The results of the studies should provide accurate estimates of the public health burden of AKI, CKD, and ESRD; their risk factors; and comorbid conditions. This information should also improve the quality of therapy provided to patients. In addition, these efforts should also focus on the special needs of refugees in countries where human-engendered and natural disasters have occurred.

The entire international nephrology community agrees that improving existing diagnostic methods and establishing preventive strategies for the detection and treatment of kidney diseases at the earliest possible stage is of utmost importance, especially in countries with limited resources or health expenditures. Therefore, in order to achieve these goals, ME countries need to invest in (1) training qualified nephrologists and medical personnel; (2) public education and campaigns for lifestyle modification to combat obesity, diabetes mellitus, and proper use of over-the-counter drugs; (3) premarital genetic counseling to decrease the burden of genetic diseases; (4) vigorous treatment of comorbid conditions that include infectious diseases and strategies for preventing dehydration in tropical ME countries; and (5) use of low-cost, generic medication.

Because transplantation is the most cost-effective treatment for established ESRD, ME countries also need to create a societal environment that motivates and encourages its population to support organ donation for transplantation in patients with ESRD. Encouraging organ donation through deceased donors, living-related donors, and paired-exchange kidney transplantation programs, as well as organ sharing among the MESOT member states, will enable ME countries to reach national sufficiency for organ transplantation. The establishment of such programs will then help to reduce the long waiting lists in each ME country and combat unethical commercial kidney transplantation.[219,248,252]

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